Clinical Study Protocol

Study Title:	A Multicenter, 2-Cohort Trial to First Assess the Pharmacokinetic and Safety Profile of a Single Dose of ZX008 (Fenfluramine Hydrochloride) Oral Solution When Added to Standard of Care (Cohort 1), Followed by a Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome (Cohort 2)
Study Number:	ZX008-1504
Study Product:	Fenfluramine Hydrochloride Oral Solution; ZX008
IND Number:	125797
EudraCT Number:	2016-000474-38
Sponsor:	Zogenix International Limited A wholly owned subsidiary of Zogenix, Inc. Siena Court, Broadway Maidenhead, SL6 1NJ, UK
Sponsor's Medical Representative	Arun Mistry, MBChB MRCP (UK) Medical Director
Date (version) of Study Protocol:	2 February 2018 (Protocol Amendment 3.3 [USA/CN]) 21 June 2017 (Protocol Amendment 2.3.8 [USA/CN]) 27 March 2017 (Protocol Amendment 2.3.1.1 [USA/CN])[a] 20 February 2017 (Protocol Amendment 2.3.1 [USA/CN])[a] 29 December 2016 (Protocol Amendment 2.3 [US/UK/CN]) 30 September 2016 (Protocol Amendment 1.1, Version 3.0)

25 May 2016 (Amendment 1, Version 2.0)

08 February 2016 (Version 1.0)

[a] Amendments 2.3.1 and 2.3.1.1 were internal amendments at the Sponsor and not released to the Investigative Sites

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator Study File. This list will be updated by the Sponsor or the Sponsor's agent and provided to study sites as needed.

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SIGNATURE OF SPONSOR

Study Number: ZX008-1504

Study Title: A Multicenter, 2-Cohort Trial to First Assess the Pharmacokinetic and Safety Profile of a Single Dose of ZX008 (Fenfluramine Hydrochloride) Oral Solution When Added to Standard of Care (Cohort 1), Followed by a Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome (Cohort 2)

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Gail Farfel — (Signature)

6 Feb 2018 — (Date [Day/Month/Year])

(Signature)

07 FEB 2018 — (Date [Day/Month/Year])

SIGNATURE OF COORDINATING INVESTIGATOR

Study Number: ZX008-1504

Study Title: A Multicenter, 2-Cohort Trial to First Assess the Pharmacokinetic and Safety Profile of a Single Dose of ZX008 (Fenfluramine Hydrochloride) Oral Solution When Added to Standard of Care (Cohort 1), Followed by a Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome (Cohort 2)

Coordinating Investigator:

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07/FEB/2018

(Date [Day/Month/Year])

SIGNATURE(S) OF PRINCIPAL INVESTIGATOR(S)

Study Number: ZX008-1504

Study Title: A Multicenter, 2-Cohort Trial to First Assess the Pharmacokinetic and Safety Profile of a Single Dose of ZX008 (Fenfluramine Hydrochloride) Oral Solution When Added to Standard of Care (Cohort 1), Followed by a Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome (Cohort 2)

I have read this study protocol, including all appendices. By signing this study protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Name and affiliation to be filled out by the investigator

Principal Investigator

Name and affiliation: _____

_____

_____ _____

(Signature) (Date [Day/Month/Year])

LIST OF ABBREVIATIONS

ABBREVATION	DEFINITION
AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve from time zero to time=t
BID	bis in die; two times per day
BMI	body mass index
BMS	BioMedical Systems, Inc.
BRIEF	Behavior Rating Inventory for Executive Function
BRIEF-P	Behavior Rating Inventory for Executive Function, Preschool Version
C-SSRS	Columbia-Suicide Severity Rating Scale
CBD	cannabidiol
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement
CLB	clobazam
CRU	Clinical Research Unit
CT	computed tomography
CYP	cytochrome P450
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EOS	end of study
EPAR	European Public Assessment Report
EQ-5D-5L	standardized measure of health status
ET	early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase or gamma-glutamyl transpeptidase
GH	growth hormone
GMP	Good Manufacturing Practices
GP	general practitioner
HRQOL	health-related quality of life
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDSMC	Independent Data and Safety Monitoring Committee

ABBREVATION	DEFINITION
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IMP	investigational medicinal product
IPCAB	International Pediatric Cardiology Advisory Board
IQR	inter quartile range
IRB	Institutional Review Board
IU	international unit
IVR	Interactive Voice Randomization
IWR	Interactive Web Response (System)
KD	ketogenic diet
kg	kilogram
LH	luteinizing hormone
LLN	lower limit of normal
MCSF	mean convulsive seizure frequency
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg/day	milligram per kilogram per day
mITT	modified Intent-to-Treat
mL	milliliter
N-CLB	n-desmethylclobazam
MRI	magnetic resonance imaging
PBPK	Physiologically-based pharmacokinetics
PedsQL	Pediatric Quality of Life Inventory
PBPK	physiologically-based pharmacokinetics
PK	pharmacokinetics
PP	per protocol
QoL	quality of life
QOLCE	Quality of Life in Childhood Epilepsy
QTcF	corrected QT interval using Fredericia method
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SD	standard deviation
SE	status epilepticus
SMEI	severe myoclonic epilepsy of infancy
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy
T + M	Titration plus Maintenance Periods
THC	tetrahydrocannabinol
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America

ABBREVATION	DEFINITION
VNS	vagal nerve stimulator/stimulation
VPA	valproate; sodium valproate; valproic acid
ZX008	fenfluramine hydrochloride oral solution

STUDY SYNOPSIS

<table>
<tr><td colspan="2">Study Title: A Multicenter, 2-Cohort Trial to First Assess the Pharmacokinetic and Safety Profile of a Single Dose of ZX008 (Fenfluramine Hydrochloride) Oral Solution When Added to Standard of Care (Cohort 1), Followed by a Randomized, Double-blind, Placebo-controlled Parallel Group Evaluation of the Efficacy, Safety, and Tolerability of ZX008 as Adjunctive Antiepileptic Therapy to Stiripentol Treatment in Children and Young Adults with Dravet Syndrome (Cohort 2)</td></tr>
<tr><td colspan="2">Study Number: ZX008-1504</td></tr>
<tr><td colspan="2">Study Product: Fenfluramine Hydrochloride Oral Solution, ZX008</td></tr>
<tr><td>Type of Study:
Efficacy, safety, and pharmacokinetics study</td><td>Indication Studied:
Adjunctive therapy in Dravet syndrome</td></tr>
<tr><td>Phase of Development: Phase III</td><td>Countries: Canada, France, Germany, the Netherlands, United Kingdom, United States, Spain</td></tr>
<tr><td colspan="2">Sponsor: Zogenix International Limited</td></tr>
<tr><td colspan="2">Coordinating Investigator:
Rima Nabbout, MD
Service de Neuromètabolisme
CHU Paris - Hôpital Necker-Enfants Malades
149 Rue de Sèvres
75743 PARIS
FRANCE</td></tr>
<tr><td colspan="2">Estimated Duration of Individual Subject Participation:
The duration of the participation in the study for an individual subject in Cohort 1 is expected to be up to 17 days (+15-day safety follow-up) for the pharmacokinetic (PK) evaluation. The duration of participation in the study for an individual subject in Cohort 2 is expected to be 6 weeks for the baseline period, and up to 17 weeks of double-blind treatment with ZX008 or placebo in the titration, maintenance, and taper/transition periods. Eligible participants from both Cohort 1 and Cohort 2 will be offered enrollment in a separate open-label extension trial. Subjects in Cohort 1 who choose to enroll in the separate long-term extension trial will participate in a transition period that will last up to a maximum of 24 weeks. Subjects in Cohort 2 who will continue into the open-label extension trial will participate in a transition period of 14 days. Subjects in Cohort 2 who do not participate in the open-label extension trial will undergo a taper period of 14 days, after which they will be off study medication. For subjects who do not enroll in the separate long-term extension, there will be a follow-up visit for cardiovascular safety monitoring 3-6 months after the last dose of study medication.</td></tr>
<tr><td colspan="2">Objectives:
The primary efficacy objective of this two-cohort study is:
o To demonstrate that ZX008 is superior to placebo as adjunctive therapy in the treatment of symptoms of Dravet syndrome in children and young adults based on change in the frequency of convulsive seizures between baseline and the combined Titration and Maintenance Periods (T + M) in Cohort 2.
The key secondary efficacy objectives of the study are related to Cohort 2 and include:
o To demonstrate that ZX008 is superior to placebo on the following endpoints:
– The proportion of subjects who achieve a ≥ 50% reduction from baseline in convulsive seizure frequency.</td></tr>
</table>

- The longest convulsive seizure-free interval.

See Statistical Methods (Section 10.5.1.3) for hierarchical testing procedure.

Additional secondary efficacy objectives of the study (Cohort 2) are:

- To demonstrate that ZX008 is superior to placebo on the following endpoints:
  - The number of convulsive seizure-free days.
  - The proportion of subjects who achieve ≥ 25% or ≥ 75% reductions from baseline in convulsive seizure frequency.
  - The change from baseline in non-convulsive seizure frequency.
  - The change from baseline in convulsive + non-convulsive seizure frequency.
  - The incidence of rescue medication usage.
  - The incidence of hospitalization to treat seizures.
  - The incidence of status epilepticus (SE).
  - The change from baseline in health-related quality of life (HRQOL) measured using the Pediatric Quality of Life Inventory™ (PedsQL) Generic Core Scale.
  - The change from baseline in PedsQL Family Impact module score.
  - Change from baseline in subjects' quality of life measured using the Quality of Life in Childhood Epilepsy (QOLCE)
  - The change from baseline in the HRQOL of the parent/caregiver using the standardized measure of health status (EQ-5D-5L) scale.
  - The change from baseline on the impacts of the condition on parents and the family using the PedsQL family impact module.
  - Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the principal investigator.
  - CGI-I rating, as assessed by the parent/caregiver.

The PK objectives of this study include:

- To assess the PK profile of ZX008 administered as a single oral dose with clobazam (CLB) + valproate (VPA) and with CLB + VPA + stiripentol (STP)
- Model PK of ZX008 in single and multiple dose regimens using fenfluramine/nor-fenfluramine concentration-time data from subjects in Cohorts 1 and 2

Exploratory objectives of this study (Cohort 2) include:

- To assess the change from baseline in health and social care resource use. These measures include planned and unplanned hospital visits, use of ambulances, general practitioner (GP) visits, speech and language therapy utilization, occupational and physical therapy utilization.
- Change from baseline in sleep quality.
- Change from baseline in mealtime behavior.
- Effect of study medication on sleepiness (Karolinska Sleepiness Scale).
- Assessment of a Dravet syndrome composite endpoint, which will include core objective (eg, seizure frequency) and subjective (eg, behavior, sleepiness, etc) patient-relevant outcome measures.

The safety objectives of the study are:

- Cohort 1: To evaluate the safety and tolerability of ZX008 as a single dose when added to standard of care treatment for Dravet syndrome (CLB + VPA; CLB + VPA + STP).
- Cohort 2: To compare the safety and tolerability of ZX008 to placebo with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate, temperature, and respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), body weight. Cognitive function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the Brief Rating Inventory Executive Function (BRIEF).

Methodology:
This is a multicenter, 2-cohort trial to first assess the PK and safety profile of a single dose of ZX008 (fenfluramine hydrochloride) oral solution when added to a standard treatment regimen for Dravet syndrome (ZX008 0.2mg/kg + CLB + VPA; ZX008 0.4 mg/kg + CLB + VPA; or ZX008 0.2 mg/kg + CLB + VPA + STP [Cohort 1]), followed by a randomized, double-blind, placebo-controlled parallel group evaluation of the efficacy, safety, and tolerability of ZX008 as adjunctive therapy in pediatric and young adult subjects with Dravet syndrome (Cohort 2). Approximately 2-3 sites in France and the Netherlands will enroll into Cohort 1; up to approximately 30 study sites in France, the Netherlands, United Kingdom, Canada, United States, Spain, and Germany will enroll subjects for Cohort 2.

This is a two-cohort study. Subjects will only be allowed to participate in one of the two cohorts. Cohort 1 will be enrolled in the open-label single-dose PK phase of the study to evaluate potential drug-drug interactions between ZX008 and CLB + VPA and between ZX008 and CLB + VPA + STP. Twenty subjects will be allocated to receive one of three dosing regimens 1) a single dose of ZX008 0.2 mg/kg + CLB+VPA [N=5], 2) a single dose of ZX008 0.4 mg/kg + CLB +VPA [N=5], or 3) a single dose of ZX008 0.2 mg/kg + CLB + VPA+ STP [N=10]. Allocation to each treatment group will be stratified by age (< 6 year of age; ≥ 6 years of age). Subjects will be confined to the clinical research unit (CRU) starting on the morning of dosing (Day 1) and will remain in the unit through the 12-hour post-dose blood draw. Blood sample collections for PK (4 mL per sample) will be obtained in the CRU prior to dosing (pre-dose), and at 2, 4, 8, and 12 hours post-dose. A final blood sample for PK analysis will be performed on Day 2 (24-36 hours post-dose), and a seizure diary will be provided. Parents/caregivers of subjects in Cohort 1 will use a diary daily to record the number/type of seizures and use of rescue medication until Day 15. Subjects will return to the clinic on Day 15 and following completion of this PK portion of the study, eligible subjects will be offered enrollment in a separate open-label extension trial and entered into a transition period where they will receive a fixed dose of ZX008 0.2 mg/kg/day for up to 24 weeks. The PK and safety data from Cohort 1 and Study ZX008-1505 have been used to inform the dose of ZX008 to be used in Cohort 2. Follow-up cardiovascular safety assessments, including ECG and ECHO, will be performed 3-6 months following the last dose of study medication. A schedule of assessments is provided in Table 1.

Participants in Cohort 2 will be enrolled in the multicenter, double-blind, parallel-group, placebo-controlled portion of the study to assess the efficacy and safety of ZX008 as adjunctive therapy of seizures in children and young adults with Dravet syndrome. The 6-week Baseline Period will consist of the establishment of initial eligibility during a screening visit followed by an observation period where subjects will be assessed for baseline seizure activity based on recordings of daily seizure

activity entered into a diary. Upon completion of the Baseline Period, subjects who qualify for the study will be randomized (1:1) in a double-blind manner to receive ZX008 (at a dose of 0.5 mg/kg/day; maximum dose 20 mg/day) or placebo. Randomization will be stratified by age group (< 6 years, ≥ 6 years) to ensure balance across treatment arms, and at least 40% of subjects will be in each age group. Titration will occur in 3 steps starting with a 0.2 mg/kg/day dose of ZX008 (or placebo equivalent) on Study Days 1-7, increased to a dose of 0.4 mg/kg/day on Study Days 8-14, and then increased to a dose of 0.5 mg/kg/day on Study Days 15-21. The duration of the Titration Period is 21 days, and the maximum daily dose at any point is 20 mg/day. Following titration, subjects will continue treatment with the assigned dose of ZX008 0.5 mg/kg/day or placebo over a 12-week Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is a maximum of 15 weeks. At the end of the Maintenance Period (or early discontinuation), all subjects will enter either a taper or transition period based on whether they exit the study or are enrolled in the separate long-term open-label extension trial, respectively. PK samples will be collected during the Follow-Up visit for subjects who will be entering the open-label extension. A follow-up ECG and ECHO will be performed 3-6 months after study drug discontinuation for early termination, or for those subjects who complete the study but do not enter the open-label extension trial Cohort 2 only).

Parents/caregivers of subjects in Cohort 2 will use a diary daily to record the number/type of seizures, dosing, and use of rescue medication. A schedule of assessments is provided in Table 2.

External Individuals and Committees: The ZX008 clinical program will employ an Independent Data and Safety Monitoring Committee (IDSMC) that will be responsible for safety oversight. A separate International Pediatric Cardiology Advisory Board (IPCAB) will monitor the cardiac safety of the ZX008 clinical trials. ECGs and Doppler ECHOs will be centrally read (Biomedical Systems, Inc.) and interpreted under blinded conditions using pre-specified criteria, and if necessary, with review by the IPCAB. The IDSMC will be informed of the dose selected for Cohort 2.

Number of Subjects:
Cohort 1: Approximately 25 subjects will be screened to ensure 18-20 subjects enter the study and complete all PK assessments. Subjects who discontinue prior to completion of all study-related procedures may be replaced.
Cohort 2: Approximately 115 subjects will be screened to randomize approximately 90 subjects. Each clinical site will not randomize more than a maximum of 8-10 subjects without prior consent from the Sponsor. Subjects who discontinue from the clinical investigation for any reason will not be replaced.

Inclusion and Exclusion Criteria
Inclusion Criteria: Subjects must meet all of the following inclusion criteria to be enrolled into the study:

1. Subject is male or non-pregnant, non-lactating female, age 2 to 18 years, inclusive as of the day of the Screening Visit. 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 (see Section 4.4), which includes abstinence, while being treated on this study and for 90 days after the dose of study drug.

2. Subject must have documented medical history to support a clinical diagnosis of Dravet syndrome, where convulsive seizures are not completely controlled by current antiepileptic drugs (AEDs).
3. Subjects must meet all of the following 5 criteria:
    a. Onset of seizures in the first year of life in an otherwise healthy infant.
    b. A history of seizures that are either generalized tonic-clonic or unilateral clonic or bilateral clonic, and are prolonged.
    c. Initial development is normal.
    d. History of normal brain magnetic resonance imaging (MRI) without cortical brain malformation.
    e. Lack of alternative diagnosis.
4. Subjects must meet at least one of the following 3 criteria:
    a. Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal has developed after the first seizure type.
    b. Prolonged exposure to warm temperatures induces seizures and/or seizures are associated with fevers due to illness or vaccines, hot baths, high levels of activity and sudden temperature changes and/or seizures are induced by strong natural and/or fluorescent lighting, as well as certain visual patterns.
    c. Genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis.)
5. Subject must have had ≥ 4 convulsive seizures (tonic-clonic, tonic, clonic) per 4-week period for 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes **[Cohort 2 only].**
6. All medications or interventions for epilepsy (including ketogenic diet [KD] and vagal nerve stimulation [VNS]) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
7. Subject must be receiving a therapeutically relevant and stable dose of CLB, VPA, and STP for at least 4 weeks prior to screening and are expected to remain stable throughout the study **[Cohort 2 only]**. (In some cases, subjects who are contraindicated for VPA or CLB may be enrolled in Cohort 2. Subjects in these cases must be receiving a therapeutically relevant and stable dose of STP and VPA [if contraindicated for CLB] or STP and CLB [if contraindicated for VPA]. Each subject must be reviewed with the Medical Monitor and sponsor before initiating screening. The decision to allow enrollment of these subjects is at the sole discretion of the sponsor.)
8. Subject must be receiving a stable dose of CLB and VPA, administered twice daily (BID), to be eligible for **Dose Regimen 1 and 2** or subject must be receiving a stable dose of CLB, VPA, and STP, administered BID, to be eligible for **Dose Regimen 3 [Cohort 1 only].**
9. Subject agrees to provide a buccal swab for CYP2D6 (cytochrome P450 2D6) genotyping.
10. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
11. Subject has provided assent in accordance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements, if capable.

12. Subject's parent/caregiver is willing and able to be compliant with all study requirements and visit schedule. Subject's parent/caregiver must also be willing and able to be compliant with diary completion and study drug accountability.

Exclusion Criteria: Subjects meeting any of the following exclusion criteria must not be enrolled into the study:

1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication.
2. Subject has pulmonary arterial hypertension.
3. Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke.
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. Subject has a current or past history of glaucoma.
6. Subject has moderate or severe hepatic impairment.
    a. Asymptomatic subjects with mild hepatic impairment (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] < 2x the upper limit of normal (ULN) and no elevations of gamma-glutamyltransferase [GGT], alkaline phosphatase, or total bilirubin indicative of more than mild hepatic impairment), 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 **[Cohort 1 only]**.
    b. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x 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 **[Cohort 2 only]**.
7. 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; triptans, atomoxetine, or other centrally-acting noradrenergic agonist; or cyproheptadine (see Appendix 1). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)
8. Subject is currently receiving or has received STP in the past 21 days prior to Screening **(only for Cohort 1 subjects allocated to Dose Regimen 1 or 2)**.
9. Subject is currently taking carbamazepine, oxcarbazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days as maintenance therapy.
10. Subject is unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges, and their juices beginning with the Baseline Period and throughout the study.
11. Subject has positive result on urine tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at the Screening Visit.
12. Subject has participated in another clinical trial within the past 30 days.
13. Subject is currently receiving an investigational product.
14. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.

15. 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.

Randomization Inclusion Criteria [Cohort 2]: Subjects must meet all of the inclusion criteria above plus the following criteria, to be randomized or allocated to study medication:

1. Subject has been approved for study inclusion by the Epilepsy Study Consortium.
2. Subject does not have a cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination, including but not limited to trace mitral or aortic valve regurgitation, or signs of pulmonary hypertension, and is approved for entry by the central cardiac safety reader.
3. Subject demonstrates a stable baseline with ≥ 6 convulsive seizures during the 6-week Baseline Period, with a minimum of 2 in the first 3 weeks and 2 in the second 3 weeks.
4. Subject's parent/caregiver has been compliant with diary completion during the Baseline Period, in the opinion of the Investigator (eg, at least 90% compliance).

Study Product, Dose, and Mode of Administration:
ZX008 is supplied as an oral solution in concentrations of 1.25, 2.5, and 5 mg/mL.

Cohort 1: Subjects are to be dosed orally with 1 of 3 regimens:

- Regimen 1: a single dose of ZX008 0.2 mg/kg + CLB +VPA
- Regimen 2: a single dose of ZX008 0.4 mg/kg + CLB + VPA, or
- Regimen 3: a single dose of ZX008 0.2 mg/kg + CLB + VPA + STP

Subjects assigned to Regimen 1 or 2 will be allocated to treatment (using a stratified randomization based on age) with either ZX008 0.2 mg/kg or ZX008 0.4 mg/kg together with their usual dose of CLB + VPA. Stratified randomization will ensure that both Regimens 1 and 2 have at least 2 subjects < 6 years old and at least 2 subjects ≥ 6 years old. Subjects assigned to Regimen 3 will receive ZX008 0.2 mg/kg + CLB + VPA + STP. At least 5 subjects will be allocated to each pre-defined age group (< 6 years old and ≥ 6 years old).

Background medications: On the day prior to dosing, the parent/caregiver will be reminded to bring the subject's usual epilepsy medications (CLB + VPA or CLB + VPA + STP) to the CRU (in addition to any other permitted epilepsy medications), for morning and evening administration on the day of dosing.

Subjects who wish to participate in the open-label extension trial, will enter the transition period and will receive ZX008 0.2 mg/kg/day together with their usual dose of CLB + VPA or CLB + VPA + STP. Study medication will be administered twice a day (BID) in equally divided doses with food.

Cohort 2: Subjects will be randomized to receive ZX008 (0.5 mg/kg/day with a maximum dose of 20 mg/day) or placebo. Study medication will be administered BID in equally divided doses with food.

Reference Product, Dose, and Mode of Administration:
Cohort 1: not applicable
Cohort 2: matching ZX008 placebo is supplied as an oral solution.

Duration of Treatment:
Cohort 1: All subjects will receive a single dose of study medication (ZX008 0.2 mg/kg + CLB +VPA or ZX008 0.4 mg/kg + CLB + VPA or ZX008 0.2 mg/kg + CLB + VPA + STP) in the PK evaluation portion of the study. After completion, eligible subjects who intend to enroll in the separate open-label extension trial, will enter a transition period at a fixed dose of ZX008 0.2 mg/kg/day for up to 24 additional weeks. Follow-up cardiovascular safety assessments, including ECG and ECHO, will be performed 3-6 months following the last dose of study medication.

Cohort 2: All subjects will receive ZX008 or matching placebo in addition to their stable AEDs for 15 weeks including the titration period through to the end of the Maintenance Period. After completion of the Maintenance Period, eligible subjects may enroll in the open-label extension trial. Subjects who do not enroll in the open-label extension trial will undergo a 14-day taper off of study medication (doses will be administered in a blinded fashion, and will be decreased in 4-day dose steps). For subjects who enter the open-label extension trial, transition will occur in 7-day dose steps over 14 days. Follow-up cardiovascular safety assessments, including ECG and ECHO, will be performed 3 to 6 months following the last dose of study medication.

Criteria for Evaluation:
Cohort 1
Pharmacokinetics: Blood samples for PK assessment of fenfluramine and its metabolite (norfenfluramine), STP, CLB and its metabolite (n-desmethylclobazam [N-CLB]), and valproic acid (VPA) will be obtained from subjects according to the schedule in Table 1 (a total of 6 samples per subject).

Safety: PK portion of the study: AEs, physical examination, vital signs, ECG, clinical laboratory parameters (standard hematology, clinical chemistry, urinalysis). Transition period: AEs, laboratory safety parameters (hematology, chemistry, urinalysis), vital signs (blood pressure, heart rate, temperature, and respiratory rate), physical examination, neurological examination, 12-lead ECGs,

Doppler ECHOs, and body weight. Cognitive Function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the BRIEF.

Cohort 2

Efficacy:

- Number of seizures by type
- Convulsive seizure-free interval
- QOLCE to measure subject's quality of life
- PedsQL Generic Core Scale to measure changes in HRQOL of the subject
- HRQOL of parent/caregiver using the EQ-5D-5L scale
- Impact of condition on parent/caregiver using PedsQL Family Impact Module
- Duration of prolonged seizures (seizure type that, during baseline, had duration > 2 minutes)
- Number of episodes of SE
- Number of instances of rescue medication use and number of doses
- Number of inpatient hospital admissions due to seizures
- CGI-I score assessed by the principal investigator
- CGI-I score assessed by the patient/caregiver

Safety: AEs, laboratory safety parameters (hematology, chemistry, urinalysis), vital signs (blood pressure, heart rate, temperature, and respiratory rate), physical examination, neurological examination, 12-lead ECGs, Doppler ECHOs, and body weight. Cognitive Function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the BRIEF.

Pharmacokinetics: Four sequential blood samples will be collected during Visit 13 for steady-state PK. Fenfluramine /nor-fenfluramine concentration-time data from subjects enrolled in Cohorts 1 and 2 will be used to model PK of ZX008 in single and multiple dose regimens.

Exploratory:

- Health and social care resource use including GP visits, speech and language, occupational and physical therapy, in addition to acute hospital and institutional length of stay, loss of work, etc.
- Change in sleep quality assessed by the patient/caregiver
- Change in mealtime behavior assessed by the patient/caregiver
- Sleepiness assessed by the patient/caregiver using the Karolinska Sleepiness Scale
- Composites endpoints that combine objective and subjective measures.

Sample Size Determination:

No formal hypothesis tests are planned for the PK endpoints studied in Cohort 1. Thus, the sample size for Cohort 1 is based on practical considerations including the expected availability of appropriate subjects. The PK data from Cohort 1 will be used in combination with physiologically-based PK (PBPK) models that are being developed using robust data from adults and from existing PBPK models for the concomitant medications. In this way, the data from ZX008-1504 will be leveraged with existing PK information on fenfluramine, STP, CLB, and VPA to confirm the expectations derived from the mechanism-based PBPK models. Analysis of the data in this way allows for the confirmation of the appropriateness of the extension of the PBPK model from adults to

children and a robust assessment of the potential for a drug-drug interaction between ZX008 and STP while limiting exposure to a smaller number of patients. The 20 subjects targeted for the PK phase of the study is expected to be sufficient to allow for the extension of the PK information gained in the ongoing PK study in adults and existing PBPK models to pediatric patients with Dravet syndrome.

The sample size for Cohort 2 is based on results from Study 1, the randomized, placebo-controlled study in subjects with Dravet syndrome sponsored by Zogenix. The standard deviation (SD) of the percentage change in seizure frequency from baseline to the end of study (Day 99) was 50% for the 0.8 mg/kg/day group and 69% for the 0.2 mg/kg/day group. For the sample size calculation for Cohort 2, the SD is assumed to be intermediate between the SDs observed in the high and low dose groups in Study 1. Assuming an SD of 58, and using a two-sided test at the α=0.05 significance level, a sample size of 45 subjects per treatment group affords 90% power to detect a difference in mean change in seizure frequency from baseline of 40 percentage points. Thus, the total sample size for Cohort 2 is planned to be approximately 90 subjects (45 per arm).

Statistical Methods:

Efficacy

Efficacy analyses will be performed only on subjects enrolled in Cohort 2. The primary efficacy endpoint is the change in the mean convulsive seizure frequency (MCSF) per 28 days during the T + M periods compared with Baseline. The MCSF will be calculated from all available data collected during the Baseline and treatment periods. The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with treatment group (ZX008 or placebo) and age group ($<$ 6 years, $\geq$ 6 years) as factors, and with baseline frequency as a covariate. The primary analysis will compare the ZX008 group to the placebo group using a two-sided test at the alpha=0.05 level of significance. The primary endpoint will also be analyzed using a nonparametric method and if normality assumptions are not met, the results of the nonparametric analysis will be used for evaluation of the primary endpoint. An additional analysis will be performed to assess the sensitivity of the primary analysis to changes in concomitant AED medications that may occur during the course of the trial. Specifically, the primary analysis will be repeated with a factor added to indicate whether a subject had a change in concomitant AED medication during the T + M period.

Safety

All safety data for Cohort 2 will be appropriately analyzed by treatment group. The number and percentage of subjects with AEs will be displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries in terms of severity and relationship to study drug will also be provided. Adverse events of special interest (AESI) and serious AEs (SAEs) will be summarized separately in a similar manner. Laboratory tests, vital signs, physical examinations, neurological examinations, ECG, Doppler ECHO, Columbia-Suicide Severity Rating Scale (C-SSRS), Tanner Staging results, etc, will be summarized appropriately, by treatment. An additional AE summary will be produced for all subjects in Cohort 1.

Pharmacokinetics

All data from Cohort 1 will be evaluated using population PK analysis methods, which will be described in detail in a separate PK analysis plan. While the approaches will be similar for all analytes of interest (fenfluramine/norfenfluramine, CLB/n-desmethylclobazam, VPA, and STP), they will be tailored to the availability of previous PK information and/or existing PK models. Summary statistics will be presented by treatment group and sampling time. Treatment groups will be compared using geometric mean ratios where appropriate.

Table 1. Schedule of Assessments

Study Assessments	Screening		(Hours relative to administration of study medication)										
			Day 1					Day 2		Transition Period		EOS/ ET	Cardiac Follow-up
Visit number	1	2	3					4	5	Phone 6, 8, 10, 12, 14, 16	7, 9, 11, 13, 15	17	18, 19
Study Day	-14 to -2	–1	Predose 0	2	4	8	12	24-36	15[a]	29, 57, 85, 113, 141, 169	43, 71, 99, 127, 155	183	3-6 mos post last dose
Informed Consent	X												
Inclusion/ Exclusion	X	X											
Medical History	X	X											
Demographics	X												
Complete neurological history and examination	X											X	
Neurological examination, abbreviated									X		X		
Epilepsy history	X												
Epilepsy status (number/type/duration seizures per month)	X								X		X	X	
Physical Examination, complete	X	X[b]										X	
Physical Examination, abbreviated									X		X		
Prior medications	X												
Body Weight, Height, BMI	X	X[c]									X	X	
12-lead ECG	X										X[d]	X	
Echocardiogram	X										X[d]	X	
Urine Pregnancy Test	X	X							X		X	X	
Clinical Laboratory Tests	X	X[e]									X	X	
Whole blood CBD	X	X[e]									X	X	
Urine THC panel	X	X[e]									X	X	
Buccal swab for CYP2D6 genotyping	X												
Epilepsy Genotype Panel	X[k]												
Vital Signs[f]	X	X	X	X		X		X			X	X	
Study Drug Administration			X						X				
PK Sampling[g]			X	X	X	X	X	X					
Dispense Seizure Diary								X	X		X		

Table 1. Cohort 1: Schedule of Assessments (continued)

Study Assessments	Screening		(Hours relative to administration of study medication)							Transition Period		EOS/ ET	Cardiac Follow-up
			Day 1					Day 2					
Visit number	1	2	3					4	5	Phone 6, 8, 10, 12, 14, 16	7, 9, 11, 13, 15	17	18, 19
Study Day	-14 to -2	–1	Pre-Dose, 0	2	4	8	12	24-36	15[a]	29, 57, 85, 113, 141, 169	43, 71, 99, 127, 155	183	3-6 mos post last dose
Review Seizure Diary									X	X	X	X	
Study Medication									D	R	C/R/D	C/R	
Concomitant Medications	X	----------X[b]----------											
Adverse Events		----------X----------											X[i]
Adverse Events of Special Interest									----------X----------				X
PEDsQL Generic Core Scale									X		X	X	
PedsQL Family Impact Module									X		X	X	
Sleep quality and mealtime behavior questions									X		X	X	
Karolinska Sleepiness Scale									X		X	X	
BRIEF									X		X	X	
QOLCE									X		X	X	
Healthcare utilization questions									X	X	X	X	
CGI-I (assessed by parent/caregiver)											X	X	
CGI-I (assessed by principal investigator)											X	X	
EQ-5D-5L (QoL of parent/caregiver)									X		X	X	
Tanner Staging (for subjects > 7 years old)									X		X[l]	X	
C-SSRS									X		X[j]	X	
Plasma sample for background AED									X		X[j]	X	

AED=antiepileptic drug; BMI=body mass index; BRIEF=Behavior Rating Inventory of Executive Function; C=Collect; CBD=cannabidiol; ; CGI-I=Clinical Global Impressions – Improvement; C-SSRS+Columbia Suicide Severity Rating Scale; CYP2D6=cytochrome P 450 2D6; D=Dispense; ECG=electrocardiogram; ECHO=echocardiogram; EOS=end of study; ET=early termination; EQ-5D-5L=standardized measure of health status; mos=months; PedsQL=Pediatric Quality of Life Inventory; PK=pharmacokinetics; QoL=quality of life; QOLCE=Quality of Life in Childhood Epilepsy; R=Review; THC=tetrahydrocannabinol

1. Day 15 ± 1. For all subjects including those who discontinued early from the study,
2. Symptom-directed physical examination performed at the investigator's discretion
3. Weight and BMI only
4. The Week 6 ECHO must be performed any time between Study Day 45 and Study Day 69. The Week 12 ECHO must be performed any time between Study Day 87 and Study Day 111; if a subject discontinues early from the study, the ECHO should be scheduled as soon as practical. If the Week 6 or Week 12 ECHO was completed ≤ 30 days prior to early termination, the Visit 17 ECHO will not be performed provided the parent/guardian agrees to bring the subject to the clinic for the cardiac follow-up visit.
5. These are baseline assessments and results will not be available prior to dosing.

6. Oral temperature, blood pressure, heart rate and respiratory rate.
7. PK draws take precedence over other study procedures.
8. Record all concomitant medications.
9. Collect adverse events of special interest only
10. Visits 7, 9, and 11 (Days 43, 71, and 99, respectively) only
11. Mandatory one time collection any time during or after screening
12. Visit 11 (Day 99) only.

Table 2. Cohort 2: Schedule of Assessments

	Baseline Period[a]			Titration + Maintenance Period											
					Titration Period			Maintenance Period					EOS/ ET[b]	Follow-up	Cardiac Follow-up[c]
Study Assessments	Screening		Randomization												
Visit Number	1	2 (Phone)	3		4 (Phone or Clinic)	5	6	7 (Phone)	8	9 (Phone)	10	11 (Phone)	12	13	14
Study Day	--43 to -42 or 42 to -41	-21	-1	1	8	15	22	36	50	64	78	92	106	120	3-6 mos post last study drug dose
Informed Consent (subject and parent)	X														
Informed Consent (EQ-5D-5L QoL of parent/caregiver)	X														
Inclusion/Exclusion Criteria	X		X												
Demographics	X														
Medical/Neurological History	X														
Epilepsy history & status	X														
Collect retrospective seizure diary data	X														
Prior Medication	X		X												
Physical Examination, complete	X		X										X		X[c]
Physical Examination, abbreviated						X	X		X		X				X[c]
Neurological Examination, complete	X												X		
Neurological Examination, abbreviated			X			X	X								
Vital signs	X		X			X	X		X		X		X		
Weight, Height, BMI	X		X			X	X		X		X		X		
12-lead ECG	X		X						X				X		X[c]
Doppler ECHO	X								X[d]				X[d]		X[c]
Urine pregnancy test[e]	X		X				X		X		X		X		
Clinical laboratory evaluation (hematology/clinical chemistry/urinalysis, etc)	X		X				X		X		X		X		
Plasma sample for ZX008 PK														X[f]	
Plasma sample for background AEDs			X[g]				X[g]		X[g]				X[g]		
Buccal swab for CYP2D6 genotyping	X														
Urine THC Panel/Whole blood CBD	X		X				X		X		X		X		
Tanner Staging (for subjects > 7 years old)			X										X		
Subject Diary	D	R	C/R/D		R	C/R/D	C/R/D	R	C/R/D	R	C/R/D	R	C/R/D[h]	C/R	

Table 2. Cohort 2: Schedule of Assessments (continued)

	Baseline Period[a]			Titration + Maintenance Period											
Study Assessments	Screening		Random-ization	Titration Period				Maintenance Period					EOS/ ET[b]	Follow-up	Cardiac Follow-up[c]
Visit Number	1	2 (Phone)	3		4 (Phone or Clinic)	5	6	7 (Phone)	8	9 (Phone)	10	11 (Phone)	12	13	14
Study Day	-43 to -42 or -42 to -41	-21	-1	1	8	15	22	36	50	64	78	92	106	120	3-6 mos post last study drug dose
Epilepsy genotype panel	X[l]														
Study Medication			D		R[i]	C/R/D	C/R/D	R	C/R/D	R	C/R/D	R	C/R/D[k]	C/R	
C-SSRS	X		X				X		X		X		X		
CGI-I (assessed by parent/caregiver)						X	X		X		X		X		
CGI-I (assessed by principal investigator)						X	X		X		X		X		
Sleep quality & mealtime behavior questions							X		X		X		X		
Karolinska Sleepiness Scale			X				X		X		X		X		
BRIEF			X						X				X		
QOLCE			X						X				X		
Healthcare utilization questions	X		X			X		X		X		X	X		
PEDsQL Generic Core Scale			X						X				X		
PedsQL Family Impact Module			X						X				X		
EQ-5D-5L (QoL of parent/caregiver)			X										X		
Randomize subject			X												
First Day of Study Drug Administration				X[j]											
Open-label consent form													X		
Daily Diary Completion		X													
Concomitant Medications				X											
Adverse events	X	X													
Adverse events of special interest	X	X													X[k]

Table 2. Cohort 2: Schedule of Assessments (continued)

	Baseline Period[a]			Titration + Maintenance Period											
Study Assessments	Screening		Random-ization	Titration Period*				Maintenance Period					EOS/ ET[b]	Follow -up	Cardiac Follow-up[c]
Visit Number	1	2 (Phone)	3		4 (Phone or Clinic)	5	6	7 (Phone)	8	9 (Phone)	10	11 (Phone)	12	13	14
Study Day	-43 to -42 or -42 to -41	-21	-1	1	8	15	22	36	50	64	78	92	106	TBD	3-6 mos post last study drug dose

AED=antiepileptic drug; BMI=body mass index; BRIEF=Behavior Rating Inventory of Executive Function; C=Collect; CBD=cannabidiol; CYP2D6=cytochrome P 450 2D6; D=Dispense; ECG=electrocardiogram; ECHO=echocardiogram; EOS=end of study; ET=early termination; EQ-5D-5L=standardized measure of health status; mos=months; PK=pharmacokinetics; QoL=quality of life; QOLCE=Quality of Life in Childhood Epilepsy; R=Review; THC=tetrahydrocannabinol

a: The Baseline Period is comprised of the initial screening for the study and the assessment of baseline seizure activity recorded daily in the diary. The procedures to be completed at the Screening visit may be completed in a single day or split so that they are completed over the 2-day period (i.e., Days -43 to - 42 or Days -42 to -41).

b: Subjects who are discontinued early and those who complete the study and choose not to enroll in the separate open-label extension will be tapered off study medication over a 2-week period. Subjects who choose to continue in the separate open-label extension trial will undergo a 2-week transition period prior to enrollment.

c: Follow-up ECG, ECHO, and physical examination will be performed 3-6 months after early termination, or for those subjects who complete the study but do not enter the open-label extension trial (see Section 6.2.6).

d: The Visit 8 ECHO must be performed any time between Study Day 40 and Study Day 54. The Visit 12 ECHO must be performed any time between Study Day 90 and Study Day 113; if a subject discontinues early from the study, the ECHO should be scheduled as soon as practical. If the Study Day 43 ECHO was completed ≤30 days prior to early termination, the Visit 12 ECHO will not be performed provided the parent/guardian agrees to bring the subject to the clinic for the cardiac follow-up visit.

e: Females of child-bearing potential

f: Plasma sample for PK assessment will be conducted prior to the dose at the Follow-up visit and 1, 2, and 4-6 hours after dose administration for Subjects continuing into the open-label extension trial.

g: Plasma sample for assessment of background AED(s) will be conducted prior to the dose of AED(s) at Visits 3, 6, 8 and 12.

h: Study drug/diary dispensed for the transition for subjects entering the open-label extension trial and for tapering for subjects exiting the study.

i: Site personnel will review study medication dosing procedure (titration) with parent/caregiver.

j: Study drug administration begins in the morning of Study Day 1.

k: Only adverse events related to cardiac safety will be collected at this visit.

l: Mandatory one time collection any time during or after screening and before Visit 10.

1. INTRODUCTION

1.1 BACKGROUND INFORMATION ON INDICATION STUDIED

ZX008 (fenfluramine hydrochloride) is under clinical development for the adjunctive treatment of patients with Dravet syndrome.

Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI), is a rare and severe form of epilepsy first described by Charlotte Dravet in 1978 (Dravet 1978). The condition most commonly appears during the first year of life as frequent febrile seizures. As the condition progresses, other types of seizures typically occur, including myoclonic seizures and status epilepticus (SE) (Dravet 1978). Following the appearance of these seizures, affected children develop several co-morbid conditions including psychomotor regression, ataxia, sleep disturbance, and cognitive impairment. Intellectual impairment begins to become apparent around age 2 years due to lack of intellectual/behavioral progression. Children with Dravet syndrome often have a lack of coordination, poor development of language, hyperactivity, and difficulty relating to others (Dravet 1978; Hurst 1990). The degree of cognitive impairment appears to correlate, at least in part, with the frequency of seizures, and might be a result of repeated cerebral hypoxia. Children with Dravet syndrome also encounter a higher incidence of sudden unexpected death in epilepsy (SUDEP; Nashef 2012) than other populations with epilepsy. Indirect evidence has linked SUDEP to several possible etiologies, including seizure-induced apnea, pulmonary edema, dysregulation of cerebral circulation, and cardiac arrhythmias (Shorvon 2011), although the actual etiology remains unknown and other mechanisms have not been ruled out. The vast majority of patients who survive to adulthood are wholly dependent on around-the-clock caregivers and eventually live in institutional care homes.

1.1.1 Existing Treatment for Dravet Syndrome

Dravet syndrome is a highly treatment-resistant and refractory epilepsy syndrome. Establishment of a seizure-free condition in affected children, even with anticonvulsant drug polypharmacy, is extremely rare, since all seizure types in Dravet syndrome appear to be drug resistant, with minimal improvement on currently available anticonvulsant drug therapies (Dravet 2000; Dravet 2005). Moreover, classic anticonvulsant medications whose mechanism is via sodium channel blockade, such as phenytoin and carbamazepine, increase these children's seizure frequency and severity.

To date, only one treatment, Diacomit® (stiripentol) is approved in Europe, Canada, Japan, and Australia as adjunctive therapy in patients with SMEI (Dravet syndrome), and must be co-administered with clobazam (CLB) and valproate (VPA). Stiripentol (STP) has not been approved for use in the United States of America, but is available under compassionate use protocols at certain clinical sites.

The results of an online parent-reported survey to collect information on the demographics, clinical characteristics and use of antiepileptic medications by European patients with Dravet syndrome was recently reported (Aras 2015). The survey took place from May to June 2014 and included two hundred seventy-four patients from 15 European countries. Most patients were 4-8 years old, and 90% had confirmed mutations in SCN1A. Their epilepsy was characterized by multiple seizure types, and 45% of the population reported more than 4 tonic-clonic seizures per month. In spite of the availability of an array of antiepileptic medications, the most common drug combination was CLB, VPA, and STP, with 42% of the patients currently taking STP.

Despite treatment with multiple antiepileptic medications, emergency room admissions for SE were common during the previous 12 months. In both the total population and the subpopulation with > 4 tonic-clonic seizures per month, approximately one-third of the patients had one or more continuous, unremitting seizures requiring emergency room admission. Twenty-eight patients (10%) reported 4 or more emergency room admissions with some reporting as many as 30 admissions for SE. In addition to severe epilepsy with multiple seizure types, respondents reported several co-morbidities that extended beyond seizures, including sleep disturbances, motor impairment, and abnormal socialization. Therefore, there remains a need for new medications that provide better seizure control, as well as preserve or improve the behavioral and cognitive components of Dravet syndrome.

For over 27 years, fenfluramine has been used as an unlicensed medicine in Belgium at 2 academic medical centers, currently using an approved protocol under a Belgium Royal Decree (government approved prospective observation trial) for the adjunctive treatment of Dravet syndrome in 19 patients; the efficacy and safety of this therapeutic approach have been published in a peer reviewed journal (Ceulemans 2012; Ceulemans 2016) and reported to be favorable. Accordingly, there remains an unmet need for an approved treatment for children with Dravet syndrome.

1.1.2 Other Antiepileptic Medications

European Union, United States of America (USA), Canada, and Australia approved anti-epileptic drug (AEDs) products include VPA, topiramate, carbamazepine, oxcarbazepine, lamotrigine, benzodiazepines, phenobarbital, potassium bromide, ethosuximide, phenytoin, and vigabatrin. The treatment of Dravet syndrome frequently requires a combination of two or three of these compounds, but with continued suboptimal seizure control. It cannot be assumed that because a treatment has been shown to be effective in common seizure types, that it will be effective in Dravet syndrome. In fact, some commonly used AEDs with a sodium channel mechanism of action, such as carbamazepine, oxcarbazepine, phenytoin, and lamotrigine, can worsen seizures in Dravet syndrome.

A review of the treatment modalities used for Dravet syndrome has been published by Chiron and Dulac (Chiron and Dulac 2011). This review indicates that VPA is commonly used as a first-line agent to prevent the recurrence of febrile seizures and oral/nasal/rectal benzodiazepine is used for any long-lasting seizures. However, the authors comment that these agents are most often insufficient. These author experts state that lamotrigine, carbamazepine, and high doses of intravenous phenobarbital should be avoided because they may worsen seizures and that topiramate, levetiracetam and bromide may provide substantial efficacy as adjunctive therapy for some patients. The authors comment that there are no trials to validate the impression of any effect.

1.2 BACKGROUND INFORMATION ON STUDY PRODUCT

Zogenix has developed an oral solution formulation of fenfluramine hydrochloride, ZX008, for the adjunctive treatment of seizures in Dravet syndrome. In addition, the effects of ZX008 on a composite of symptoms that negatively impact quality of life and intellectual development will be explored. Fenfluramine is an amphetamine analogue that was approved in a large number of countries and widely prescribed as an appetite suppressant for the treatment of adult obesity.

Products containing fenfluramine and the D-enantiomer were withdrawn from the market globally after reports of heart valve disease and pulmonary hypertension in the late 1990's (Connolly 1997; CDC 1997; Wong 1998). While the risk/benefit relationship for fenfluramine is thus considered unfavorable for the treatment of obesity in adults, establishing seizure control in Dravet syndrome or any of the catastrophic childhood epilepsies might lead to a more acceptable risk/benefit profile for fenfluramine, especially if lower doses can be used successfully.

As a result of this previous extensive use of fenfluramine, there is a large body of information in the public domain concerning its pharmacology, toxicology and use in the treatment of obesity (ZX008 IB 2016). There is also a large body of information concerning its clinical safety profile.

1.3 PRECLINICAL DATA

The pharmacokinetics (PK) of fenfluramine, norfenfluramine and their respective isomers has been studied in mice, rats, dogs and humans. The PK in humans differs from that of other species, with a longer duration of exposure to both the parent and the metabolite. *In vitro* metabolism studies have shown that there are large species differences in PK and metabolism of fenfluramine after oral administration. In humans, fenfluramine is metabolized to primarily norfenfluramine. CYP1A2, CYP2B6, and CYP2D6 appear to be the predominant CYP (cytochrome P450) enzymes that metabolize fenfluramine to norfenfluramine. CYP2C9, CYP2C19 and CYP3A4 also appear to be involved, but to a lesser degree. There is also some contribution of renal clearance to the elimination of dexfenfluramine (8% - 16%) and

nordexfenflurmine (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 Food and Drug Administration's (FDA's) mechanistic static model shows that fenfluramine and its major metabolite norfenfluramine are unlikely to alter the PK of substrates of these CYP450 enzymes in the range of ZX008 doses that will be administered in this study.

A Good Laboratory Practice dose-range-finding juvenile toxicology and toxicokinetic study, which included a 3-week repeat dose main study, and histopathology of heart valves and other key organs, found no effect on heart valves or other organs.

Based on clinical signs and decreased body weight gain, the no-observed-adverse-effect-level for this study was 12 mg/kg/day. This is estimated to be equivalent to a human dose of 1.94 mg/kg/day based on body surface area, and provides a safety factor of approximately 2.4 for the serum levels of ZX008 that are anticipated in this study.

Further details on the preclinical data of ZX008 are available in the Investigator's Brochure (ZX008 IB 2016). The current version is available in the Investigator Study File.

1.4 BACKGROUND INFORMATION ON REFERENCE PRODUCT

Not applicable.

1.5 RATIONALE FOR CURRENT STUDY

There is only one treatment approved for adjunctive treatment of seizures in children with Dravet syndrome in Europe (ie, STP), and it is administered in conjunction with two other antiepileptic drugs, VPA and CLB. Further, the recent survey conducted by Aras and colleagues (Aras 2015) revealed that in spite of the availability of an array of antiepileptic medications, the most common drug combination was CLB, VPA, and STP, with 42% of the patients currently taking STP. STP inhibits several CYP450 enzymes, and drug-drug interactions with STP will need to be evaluated for any new drugs likely to be co-administered with it. The potential for a drug-drug interaction of STP with fenfluramine needs to be carefully taken into account by adjusting the dose(s) of either fenfluramine, another antiepileptic medication, or the combined antiepileptic drugs as the PK interactions might affect efficacy and tolerability. This potential interaction will be explored in Cohort 1 of this study. Given that STP acts as an inhibitor of CYP3A4, CYP1A2 and in particular CYP2C19,

in vivo in epileptic patients, it is likely that the dose of fenfluramine will need to be at the lower end of the dose range of the doses used in the Belgian study cited above (doses ranged from 0.12 – 0.9 mg/kg/day in this series). Subjects in Cohort 1 (Regimen 3) will be dosed with 0.2 mg/kg of ZX008 to evaluate the PK and safety profile of a single dose when added to the subjects' usual regimen of STP/VPA/CLB. The data for this Cohort has informed the dosing for Cohort 2. Moreover, blood samples for population PK will be collected from Cohort 2, and the fenfluramine/nor-fenfluramine concentration-time data from subjects enrolled in Cohorts 1 and 2 will be used to model PK of ZX008 in single and multiple dose regimens.

The efficacy and safety of ZX008 as adjunctive therapy added to the STP regimen for seizures in children and young adults with Dravet syndrome will be evaluated in Cohort 2. A recent study published by Aras and colleagues (Aras 2015) on 274 children with Dravet syndrome from 15 European countries, found that their epilepsy was characterized by several different types of seizures, and 45% had significant residual tonic-clonic seizures despite taking an array of antiepileptic medications. The most common drug combination in these patients was CLB, VPA, and STP, with 42% of the patients currently taking STP. Accordingly, there remains a significant unmet need for other adjunctive treatments for children and adults with Dravet syndrome.

1.6 RISK-BENEFIT ASSESSMENT

It is the Sponsor's position that fenfluramine may be an important new therapeutic for children with Dravet syndrome and that it can be safely studied in patients with Dravet syndrome given proper study designs (eg, including regular echocardiographic evaluations) and the use of independent safety monitoring committees, resulting in a favorable benefit to risk ratio for the proposed indication at the proposed doses. Additionally, fenfluramine was administered to over 500 children with neurobehavioral conditions, including autism and attention deficit hyperactivity disorder, with good safety and tolerability, most often at a 1 mg/kg dose.

Dravet Syndrome is a rare, devastating epileptic encephalopathy. The condition is marked by frequent and multiple seizure types, including SE, which begin in the first year of life and remain pharmacoresistant to currently available antiepileptic drugs (Chiron 2011). The frequent prolonged seizure activity and episodes of SE in Dravet syndrome patients, unabated by the largely ineffective available treatments, is believed to result in brain injury, and impairment of psychomotor, behavioral, and neurological development (Dravet 2011).

The mortality risk is high and childhood death is frequently caused by SUDEP. The estimated mean annual rate of SUDEP in Dravet Syndrome is 0.6%, which is significantly higher than that reported in the general population of patients with epilepsy (< 0.1%; and a mortality rate of 10% to 15% during childhood and adolescence (Skluzachek 2011).

A group in Belgium began treating Dravet syndrome patients with fenfluramine under a government compassionate use program (Belgian Royal Decree) in 2002. In 2012 these investigators reported on the use of fenfluramine in 12 patients treated until 2010. Exposure duration to fenfluramine ranged from 1–19 years. Seven of the Dravet syndrome patients who were still receiving fenfluramine treatment at the time of the last visit had been seizure-free for at least 1 year. In total, patients had been seizure-free for a mean of 6 years, 7 months (1-19 years). Fenfluramine was generally well tolerated. No patient exhibited any cardiovascular symptomatology. Regular cardiovascular follow-up, which included electrocardiograms (ECGs) and echocardiograms (ECHOs), showed no cases of pulmonary hypertension. A slight thickening of 1 or 2 heart valves was demonstrated in 2 patients (Patients 2 and 10) but these changes were stable and considered not clinically significant. Patient 2 had been on 5 mg twice daily (BID) for 2 years and Patient 10 on 20 mg once daily for 11 years.

A second more recent effectiveness and tolerability assessment of this cohort included visit data from 2010 through the end of 2014, ie, 5 years of data. More than 80% of patients had a ≥75% reduction in seizure frequency in response to fenfluramine each year of the 5-year evaluation. During this 5-year observation period, 3 patients were seizure-free for all 5 years and 5 patients were seizure-free for 2-4 years; in all, 29 of 58 (50%) patient-treatment years were seizure-free. In this 2010 to 2014 period, 5 patients had transient, mild cardiac valve thickening reported on echocardiography at only one examination which were no longer observed in all subsequent studies. One patient had valve thickening seen in the first 4 years but was not found at the most recent follow-up echocardiogram. Two patients had mild valve thickening noted on their last echocardiography, but without any clinical symptoms; (according to the investigators, these remain stable). At no point was clinically significant valve thickening observed with fenfluramine nor were there any signs of pulmonary hypertension. No patients have discontinued treatment as a result of any cardiovascular AEs.

A third recent analysis was conducted that included 7 additional patients (5 males and 2 females) who were enrolled after 2010, with data through March 2015 (Ceulemans 2015). The median starting fenfluramine dose was 10 mg per day. Mean treatment duration was 22 months. The mean seizure frequency in these 7 patients prior to initiation of fenfluramine was 11.4 per month (range 0.4 to 39.7) and at 6 months after starting fenfluramine there was a dramatic decrease with a mean of 2.6 seizures per month (range 0-6) seizures per month. Every patient's echocardiographic examinations which were normal at baseline, continued to be normal at every post-treatment assessment without any signs of valvulopathy, pulmonary hypertension or any other cardiovascular abnormality.

The dramatic long-term prospective effectiveness data described above of the Belgian cohort of Dravet syndrome patients who have now been successfully treated with fenfluramine, in some cases, for over 25 years, without any signs of clinically significant valvulopathy or reports of

pulmonary hypertension, strongly supports the potential benefit outweighs the risk in this particular patient population.

The approximate volume of blood (63.4 mL) planned for collection from Cohort 1 up to Day 15 presents no undue risk to the subjects, and will provide useful information on the PK profile of these antiepileptic medications when ZX008 is added to treatment with CLB + VPA or with CLB + VPA + STP. As noted above, the dose of ZX008 to be used in Cohort 1 will be at the low end of the dose range for subjects who are receiving STP/VPA/CLB to minimize potential side effects associated with the combination.

The 0.5 mg/kg/day, with a maximum 20 mg/day dose of ZX008 to be administered for Cohort 2 has been informed by assessment of PK and safety data derived from Cohort 1. The Independent Data and Safety Monitoring Committee (IDSMC) has been provided with the safety and PK data from Cohort 1 and have validated the methodology for the 0.5 mg/kg/day dose selected for Cohort 2. Based on previous work with ZX008 in this population, fenfluramine should provide sufficient anti-epileptic support for a sustained period of time during the study.

The safety monitoring practices employed by this protocol, including extensive cardiovascular monitoring, are adequate to protect the subjects' safety and should detect expected and unexpected treatment-emergent adverse events.

The available information suggests that the present clinical study has an acceptable risk-benefit ratio.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY EFFICACY OBJECTIVE

The primary efficacy objective of this multicenter two-cohort study is:

- To demonstrate that ZX008 is superior to placebo as adjunctive therapy in the treatment of symptoms of Dravet syndrome in children and young adults based on change in the frequency of convulsive seizures between baseline and the combined Titration and Maintenance Periods (T + M) in Cohort 2.

2.2 KEY SECONDARY EFFICACY OBJECTIVES

The key secondary efficacy objectives of the study are related to the double-blind, placebo-controlled part of the study (Cohort 2) and include:

- To demonstrate that ZX008 is superior to placebo on the following endpoints:
    - The proportion of subjects who achieve a ≥ 50% reduction from baseline in convulsive seizure frequency.
    - The longest convulsive seizure-free interval.

See Statistical Methods (Section 10.5.1.3) for hierarchical testing procedure.

2.3 ADDITIONAL SECONDARY EFFICACY OBJECTIVES

Additional secondary efficacy objectives of the study (Cohort 2) are:

- To demonstrate that ZX008 is superior to placebo on the following endpoints:
    - The number of convulsive seizure-free days.
    - The proportion of subjects who achieve ≥ 25% or ≥ 75% reductions from baseline in convulsive seizure frequency.
    - The change from baseline in non-convulsive seizure frequency.
    - The change from baseline in convulsive + non-convulsive seizure frequency
    - The incidence of rescue medication usage
    - The incidence of hospitalization to treat seizures
    - The incidence of SE

- The change from baseline in health-related quality of life (HRQOL) measured using the Pediatric Quality of Life Inventory™ (PedsQL) Generic Core Scale
- The change from baseline in PedsQL Family Impact module score
- Change from baseline in subjects' quality of life measured using the Quality of Life in Childhood Epilepsy (QOLCE)
- The change from baseline in the HRQOL of the parent/caregiver using the standardized measure of health status (EQ-5D-5L) scale
- The change from baseline on the impacts of the condition on parents and the family using the PedsQL family impact module.
- Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the principal investigator
- CGI-I rating, as assessed by the parent/caregiver

The safety objectives of the study are:

- To evaluate the safety and tolerability of ZX008 administered as a single oral dose when added to standard of care treatment for Dravet syndrome (CLB + VPA; CLB + VPA + STP) (Cohort 1)
- To compare the safety and tolerability of ZX008 to placebo with regard to AEs, laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate, temperature, and respiratory rate), ECGs, ECHOs, and body weight, and assessment of cognitive function (Cohort 2).

The PK objectives of the study are:

- To assess the PK profile of ZX008 administered as a single oral dose with CLB + VPA or with CLB + VPA + STP in subjects ages 2-18 years of age with Dravet syndrome (Cohort 1).

- Model PK of ZX008 in single and multiple dose regimens using fenfluramine/nor-fenfluramine concentration-time data from subjects in Cohorts 1 and 2.

2.4 EXPLORATORY OBJECTIVE

Exploratory objectives of this study [Cohort 1 and 2 will be evaluated separately] include:

- The change from baseline in health and social care resource use including planned and unplanned hospital visits, use of ambulances, general practitioner (GP) visits, speech and language therapy utilization, occupational and physical therapy utilization.
- Change from baseline in sleep quality.

- Change from baseline in mealtime behavior.
- Effect of study medication on sleepiness (Karolinska Sleepiness Scale).
- Assessment of a Dravet syndrome composite endpoint including seizure frequency and severity and subjective patient-relevant outcome measures (eg, behavior, sleepiness, etc) using data from the collected rating scales will be performed.

2.5 STUDY ENDPOINTS

2.5.1 Efficacy Endpoints (Cohort 2 only)

The efficacy endpoints of the study are:

- Number of seizures by type
- Convulsive seizure-free interval
- Number of instances of rescue medication use and number of doses
- Number of inpatient hospital admissions due to seizures
- Duration of prolonged seizures (seizure type that, during baseline, had duration > 2 minutes)
- Number of episodes of SE
- QOLCE to measure changes in quality of life of the subject
- HRQOL based on the PedQL Generic Core Scale
- HRQOL of the parent/caregiver using the EQ-5D-5L scale
- Impact of the condition on parents and the family using the PedsQL Family Impact Module.

2.5.2 Safety Endpoints

The safety endpoints of the study are:

- AEs
- Laboratory safety (hematology, chemistry, urinalysis)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Physical examination
- Neurological examination
- 12-lead ECGs
- Doppler ECHOs
- Body weight
- Cognitive Function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the BRIEF

2.5.3 Pharmacokinetic Endpoints

The PK endpoints of the study are:

- PK data for all analytes (fenfluramine, norfenfluramine, CLB, n-desmethylclobazam (N-CLB), VPA, and STP) for Cohort 1 will be used for PK modeling
- PK sampling for ZX008 will be performed on subjects in Cohort 2. Fenfluramine/nor-fenfluramine concentration-time data from subject enrolled in Cohorts 1 and 2 will be used to model PK of ZX008 in single and multiple dose regimens

2.5.4 Exploratory Endpoints

The exploratory endpoints of the study are:

- Health and social care resource use including GP visits, speech and language, occupational and physical therapy, in addition to acute hospital and institutional length of stay, loss of work, etc.
- Change in sleep quality assessed by the patient/caregiver
- Change in mealtime behavior assessed by the patient/caregiver
- Sleepiness assessed by the patient/caregiver using the Karolinska Sleepiness Scale
- Composites endpoints that combine objective and subjective measures

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This is a multicenter, two-cohort trial to assess the PK and safety profile of a single dose of ZX008 (fenfluramine hydrochloride) oral solution when added to Dravet syndrome treatment regimen containing VPA and CLB, with or without STP (Cohort 1), followed by a randomized, double-blind, placebo-controlled parallel group evaluation of the efficacy, safety, and tolerability of ZX008 as adjunctive therapy for seizures in children and young adults with Dravet syndrome (Cohort 2). PK and safety data from Cohort 1 from 13 subjects have been collected and evaluated together with data from Study ZX008-1505 (healthy volunteer drug-drug interaction study) and has informed the dose of ZX008 0.5 mg/kg/day, maximum 20 mg/day, to be used in Cohort 2. The current Amendment of this protocol defines the dose for Cohort 2. Approximately 2-3 sites in France and the Netherlands will be involved in the PK portion of the trial (Cohort 1). Up to approximately 30 study sites in Canada, France, Germany, Netherlands, United Kingdom, Spain, and the United States will enroll participants for Cohort 2.

Cohort 1: Subjects will attend the clinical research unit (CRU) for a screening visit up to 14 days before dosing. Eligible subjects will return to CRU on Study Day –1 for an outpatient visit. Inclusion and exclusion criteria will be confirmed, and physical exam, medical history, body weight/body mass index (BMI), vital signs, urine pregnancy test, urine tetrahydrocannabinol (THC), and whole blood cannabinol (CBD) will be obtained. The subject will be discharged from the unit or allowed to stay overnight, as required. After dinner and a light snack prior to bedtime, subjects will be fasted until the next morning. On the following day (Study Day 1), a parent/caregiver will bring the fasted subject to the CRU between 6 AM and 7 AM.

Following blood collection for clinical labs, and vital sign measurements and weight, subjects will be given a light, low fat breakfast, followed by administration of their usual epilepsy medications. Based on the assigned treatment allocation, each subject will then receive the appropriate dose of study medication (ZX008). Subjects receiving CLB and VA at screening will be stratified by age group (< 6 years of age; ≥ 6 of age) and randomly allocated to Dosing Regimen 1 (ZX008 0.2 mg/kg + CLB + VPA) or Regimen 2 (ZX008 0.4mg/kg + CLB + VPA). At least two subjects from each pre-specified age group are to be assigned to Regimen 1; and at least 2 subjects from each group are to be assigned to Regimen 2. Subjects receiving CLB and VA and STP at screening, will be assigned to Regimen 3 (ZX008 0.2 mg/kg + CLB + VPA + STP). Approximately 5 subjects from each age group (< 6 years; ≥ 6 years) should be enrolled in dosing Regimen 3. Details for each regimen are shown in Table 3.

Table 3. Cohort 1 Dosing Regimens

Dosing Regimen	Dosing on Day 1	Dose of ZX008	Age Stratification
#1	CLB + VPA + ZX008	0.2 mg/kg	[n=5]; at least 2 subjects per age group (< 6 and ≥ 6 years)
#2	CLB + VPA + ZX008	0.4 mg/kg	[n=5]; at least 2 subjects per age group (< 6 and ≥ 6 years)
#3	CLB + VPA + STP + ZX008	0.2 mg/kg	[n=10]; total of 5 subjects per age group (< 6 and ≥ 6 years)

Blood samples for PK assessment will be obtained from all subjects through 12-hours post-dose. After the last Study Day 1 blood draw (12 hours post-dose), subjects will be discharged. Twenty-four to thirty-six hours following dosing the subjects will return to the research unit for assessment of vital signs, a final PK sample and to record any adverse events that may have occurred since leaving the CRU. A seizure diary will be provided to record seizure activity between Study Day 2 and the follow-up safety visit (Study Day 15). On Study Day 15, subjects and/or caregivers will return to the CRU for follow-up, including review of diary data. At the conclusion of this portion of the study, eligible subjects from Cohort 1 will be offered enrollment in a separate open-label extension trial and if they choose to do so, they will begin transitioning to study medication (ZX008, 0.2 mg/kg/day), safety and diary data will continue to be captured and the exploratory composite endpoint components will be administered prior to commencement of transitional treatment. The duration of the transition period will not exceed 24 weeks. Subjects may enroll in the separate open-label extension trial when the dose for Cohort 2 has been selected. A schedule of assessments is provided in Table 1.

For Cohort 1 subjects, a follow-up ECHO, ECG, and symptom-directed physical examination will be performed 3-6 months after study drug discontinuation with early termination.

Cohort 2: A 6-week Baseline Period will consist of the establishment of initial eligibility during a screening visit followed by an observation period where subjects will be assessed for baseline seizure activity based on recordings of daily seizure activity entered into a diary. Upon completion of the Baseline Period, subjects who qualify for the study will be randomized (1:1) in a double-blind manner to receive ZX008 (at a dose of 0.5 mg/kg/day, maximum 20 mg/day) or placebo. Randomization will be stratified by age group (< 6 years, ≥ 6 years) to ensure balance across treatment arms, and at least 40% of subjects will be in each age group. All subjects will be titrated to their randomized dose during the Titration Period. Titration will occur in 3 steps starting with a 0.2 mg/kg/day dose of ZX008 (or placebo equivalent) on Study Days 1-7, increased to a dose of 0.4 mg/kg/day on Study Day 8-14, and then increased to a dose of 0.5 mg/kg/day on Study Days 15-21; the maximum daily dose at any point is 20 mg/day. The duration of the titration period will be 21 days.

Following titration subjects will continue treatment at their randomly assigned dose of ZX008 0.5 mg/kg/day (maximum 20 mg/day) or placebo over a 12-week Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is a maximum of 15 weeks. Parents/caregivers will use a diary daily to record the number/type of seizures, dosing, and use of rescue medication. A schedule of assessments is provided in Table 2.

At the end of the Maintenance Period (or early discontinuation), subjects who will not be entering the open-label extension will undergo a taper of 14 days, after which they will be off study medication. Subjects who will be enrolled in the separate open-label extension trial will enter a 14-day transition period.

For Cohort 2 subjects, a follow-up ECHO, ECG, and possibly physical examination will be performed 3-6 months after study drug discontinuation with early termination, or for those subjects who complete the study but do not enter the open-label extension trial.

3.2 NUMBER OF SUBJECTS

Cohort 1: Approximately 25 subjects will be screened to obtain 18-20 subjects who complete all PK assessments. Dropouts will be replaced.

Cohort 2: Approximately 115 subjects will be screened to randomize approximately90 subjects . Each clinical site will not randomize more than a maximum of 8-10 subjects without prior consent from the Sponsor.

3.3 STUDY DURATION

Cohort 1: For the PK portion of the study, the duration of participation for an individual subject is expected to be up to 32 days:

- Screening – 14 days (The screening period may be extended to ensure all screening results are reviewed for eligibility prior to dosing.)
- Day -1 CRU outpatient visit – 1 day
- Dosing/PK sampling – 2 days
- AE follow-up – 15 days
- In addition, the subject may enter a transition period until enrolment into the open-label extension trial, not to exceed 168 days (24 weeks)
- Cardiac Follow-up (ECG and ECHO) – 3-6 months after study drug discontinuation for early termination.

Cohort 2: The duration of participation in the study for an individual subject is 15 weeks of double blind therapy (T + M; not including transition or taper), plus follow-up safety visit 3 to 6 months after the last dose:

- Baseline Period – 6 weeks
- T + M Period – 21 days + 12 weeks
- Transition for subjects continuing into open-label extension trial – 14 days
- Taper for subjects not continuing into open-label extension trial – 14 days, after which they will be off study medication
- Post-Dosing Follow-up Visit – 14 days after study completion or early termination
- Cardiac Follow-up (ECG and ECHO) – 3-6 months after study drug discontinuation for early termination or for subjects who complete the study but do not enroll in the open-label extension trial

3.4 NUMBER OF STUDY CENTERS

Two to three research centers in France and the Netherlands will enroll participants for Cohort 1. Up to approximately 30 research centers in Canada, France, Germany, the Netherlands, United Kingdom, Spain, and the United States will enroll subjects for Cohort 2. Additional study centers or countries may be added if enrollment cannot be completed in a timely manner.

3.5 RATIONALE FOR STUDY DESIGN AND CHOICE OF TREATMENT

It is recognized that performing clinical studies in young children or in subjects with reduced cognitive capacity presents particular practical and ethical issues. Meeting the objectives of the study require evaluation in the patient population, ie, evaluation of PK and efficacy and safety endpoints in children with Dravet syndrome. Given the seriousness of Dravet syndrome, with onset of seizures before two years of age, and the possible consequences of current treatment limitations, the use of children with Dravet syndrome in this study is considered justified. Results from a parent-reported survey on antiepileptic medication use in the European population with Dravet syndrome demonstrate that many children with Dravet syndrome are still having seizures despite combination treatment with standard of care agents (CLB + VPA or STP + CLB + VPA); moreover, most continue to have other significant neurological and behavioral comorbidities. Adding a medication with a different mechanism of action to existing treatment increases the likelihood of a meaningful clinical response. ZX008 (fenfluramine hydrochloride), an analogue of amphetamine that increases extrasynaptic serotonin, has been shown to have a positive clinical outcome as an add-on treatment for Dravet syndrome in a case series of patients followed for more than two decades.

Current standard of care for patients with Dravet syndrome in the European Union includes treatment with a combination of antiepileptic medications, most commonly VPA, CLB,

topiramate, levetiracetam, and STP. STP (together with CLB and VPA), the only drug specifically approved for this indication, is widely prescribed by pediatric epilepsy physicians for their patients with Dravet syndrome. STP is a potent inhibitor of several CYP450 isoenzymes, including CYP2D6, and when used in combination with other antiepileptic medications may increase their plasma levels and hence increase side effects. Acknowledging that an adjunctive antiepilepsy medication marketed in Europe is likely to be taken by patients also taking STP, and that inhibition of CYP2D6 is likely to increase levels of ZX008, this study focuses first on evaluating the PK and safety profile of low doses of ZX008 when administered with a standard treatment regimen (CLB + VPA or CBA + VPA + STP) in one cohort, thus establishing the dose of ZX008 that produces serum levels when given with STP that are similar to effective doses from the Belgian experiment (Ceulemans 2012). Based on data from 13 patients in Cohort 1, and data from Study ZX008-1505 the 0.5 mg/kg/day (maximum 20 mg/day) ZX008 dose was determined as the target dose for the second cohort based on matching the exposure (AUC) of fenfluramine at 0.8 mg/kg/day (maximum 30 mg/day) without STP/CLB/VLP. The analysis leveraged physiologically-based pharmacokinetics (PBPK) models for ZX008, CLB, VLP, and STP. PK and safety data from Cohort 1, and data from Study ZX008-1505 were evaluated using the model to quantify the extent of the PK interaction between fenfluramine and the combination of CBA + VPA + STP. The 0.5 mg/kg/day ZX008 dose (maximum 20 mg/day) for Cohort 2 was selected with the goal of maintaining mean patient PK exposures within 10% of that which is expected in patients receiving 0.8 mg/kg (maximum 30 mg/day) in the absence of interacting AEDs. Data from Study ZX008-1505 showed that fenfluramine does not have a significant effect on the PK of the concomitant medications (STP/CLB/VLP).

The goal of dose selection was to predict the drug interaction on fenfluramine for subjects taking STP/CLB/VLP together. The minimum number of subjects required to provide an adequate assessment of the mean result for the purposes of selecting the Cohort 2 dose was defined as 10 subjects from all dose regimens combined; data from 13 subjects were available at the time of making a dose decision. Ten of the 13 subjects in the Cohort 1 data set were in Regimen 3, ie, they were taking all three concomitant medications required by the protocol in Cohort 2.

A PBPK model system has been developed in order to quantify the potential impact of STP, CLB, and VPA on the PK of fenfluramine. The model system has been qualified using data from Study ZX008-1505 and was shown to replicate the adult data well (i.e., the simulated ratio of fenfluramine area under the concentration-time curve [AUC] when administered alone to the fenfluramine AUC with combination therapy were very similar to the observed fenfluramine AUC ratios from Study ZX008-1505).

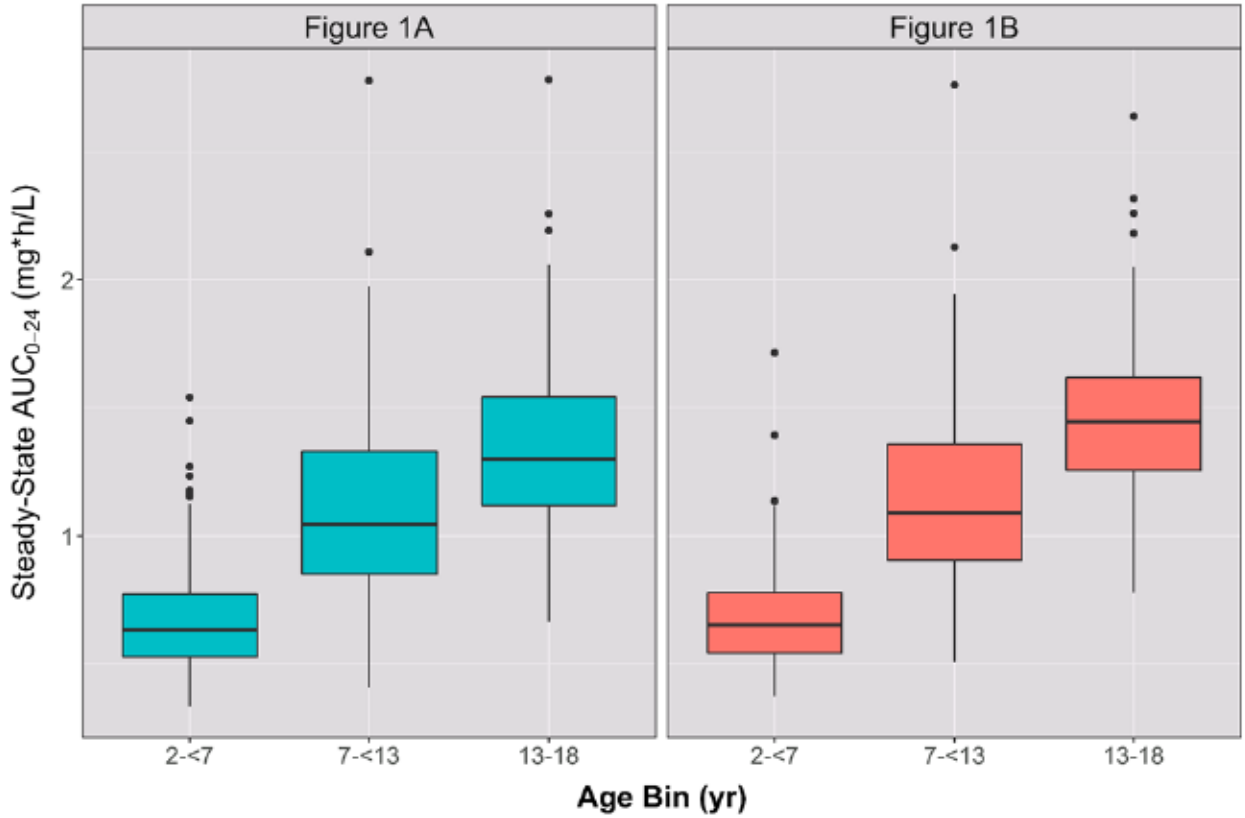
The model system was then modified for application to children. The data from Cohort 1 of ZX008-1504 was used to qualify the model system in children aged 2-18 years with Dravet syndrome. This was accomplished by simulating concentration-time profiles using the

demographic characteristics and concomitant medication dosages from the 13 subjects included in the interim analysis. In each case, patient-specific data were used, in combination with empirical estimates of variability in model parameters, to generate a median and 90% prediction interval for drug concentrations over time after the administration of the single dose of ZX008. The patient-specific data were: 1) dosing histories for ZX008, STP, and CLB, including dose, interval, and timing of doses relative to the PK sampling times, and 2) patient demographic factors such as age, sex, height, and weight. The observed fenfluramine and norfenfluramine concentrations were then compared to the predictions across all patients, stratified by treatment with or without stiripentol.

Using the modified PBPK model system, simulations were conducted to estimate drug exposure (AUC) after administration of ZX008 in a hypothetical population of children (n=1000) aged 2-18 years with height and weight appropriate for their age and sex (50% female). Exposure estimates were generated assuming all subjects were receiving STP and CLB at doses of 500 and 5 mg BID, respectively. These represent an estimate of the doses in Cohort 1 for STP and CLB. This was compared against a reference ZX008 dose of 0.8 mg/kg/day with a maximum dose of 30 mg/day to identify an appropriate matching dose.

Based upon the predicted effects of concomitant stiripentol and clobazam, the dose that best matched the exposure for the reference dose (ie, 0.8 mg/kg/day with a maximum of 30 mg/day, in the absence of stiripentol or clobazam) was 0.5 mg/kg/day with a maximum dose of 20 mg/day. Both the mg/kg and maximum dose were modified to ensure the best match of exposure in young children (0.5 mg/kg/day) as well as to ensure that individual older patients did not have excursions in exposure (20 mg/day). Figures 1A and B shows box and whisker plots of the predicted steady-state exposure as a function of age.

Figure 1A: Fenfluramine 0.8 mg/kg/day, maximum 30 mg/day, no STP or CLB; and Figure 1B: Fenfluramine 0.5 mg/kg/day, maximum 20 mg/day, STP 1000 mg/day, CLB 10 mg/day



Box and whisker plots: box represents 25th – 75th interquartile range (IQR), line in middle of the box represents the median, vertical lines (whiskers) above and below box are + and - 1.5 times the IQR, dots beyond the whiskers are outside that range. Review of safety data from the 13 subjects in study ZX008-1504 that contributed to the dose decision shows ZX008 has been well tolerated. Based on the predicted exposures, the safety profile for 0.5 mg/kg/day ZX008 (maximum 20 mg/day) in combination with STP/CLB/VPA is expected to be similar to 0.8 mg/kg/day ZX008.

Dose selection information for Cohort 2 was shared with and validated by the IDSMC (which includes a neurologist, pediatric epileptologist, general pediatrician, and pediatric cardiologist) and independent statistician. The decision on dose selection for Cohort 2 was communicated by notification with the updated protocol, informed consent document, and schedule of assessments to the Ethics Committees, Competent Authority, and Investigators. Training on the updated protocol will be provided to the investigative sites.

For both cohorts, stratifying the randomization or allocation by age group is considered appropriate because the frequency and severity of major seizures can be higher in younger subjects. The two strata in the study will be subjects aged below 6 years and subjects ≥ 6 years. The study design for Cohort 2 has incorporated a titration period to ensure subjects have adequate time to acclimate to their dose of ZX008. Following the Titration Period, subjects will enter a 12-week Maintenance Period where they will continue on their randomized dose for the remainder of the study. The 12-week duration of the Maintenance Period is in keeping with the current standard study duration for evaluating the efficacy of chronic medications. Given the individual variability in seizure frequency and seizure type in this patient population, the primary endpoint, which seeks to compare an appropriate baseline of convulsive seizure frequency to the convulsive seizure frequency following treatment, is an appropriate primary endpoint for efficacy in this population. The primary endpoint considers only convulsive seizures to improve accuracy of the measure. Secondary endpoints will evaluate all seizure types.

Subjects will receive investigational medicinal product (ZX008 or placebo) in addition to their existing antiepileptic medications at their stable doses throughout the entire study. Thus, subjects receiving placebo will not be denied active therapy; they will continue to receive their existing medications at the exact same dosages throughout the entire study. As the principal study measurement (convulsive seizures) might be considered subjective, a double-blind study design will prevent subjective bias. Upon study completion, eligible subjects from both Cohorts 1 and 2 who might derive additional benefit from ongoing treatment with fenfluramine will be able to receive ZX008 in an open-label extension trial for 1 additional year of treatment, with additional extensions if safety and efficacy are determined and the medication is not available for prescription in their country.

3.6 PREMATURE TERMINATION OF STUDY

The Sponsor can terminate the study prematurely at any time for medical or ethical reasons at individual or at all study sites. The investigator will be notified in writing, outlining the reasons for the termination. Instructions will be provided if assessments beyond those described in the study protocol need to be conducted.

If the study is terminated prematurely for any reason, the investigator should promptly inform the subjects participating at his or her study site and should ensure that appropriate alternative therapy is available and that End-of-Study procedures are conducted, as described in Section 6.1.5, Section 6.2.5.10, and Section 6.2.5.11.

All study materials including investigational medicinal product (IMP) and completed, partially completed, and blank documentation, except documents needed for archiving requirements, will be returned to the Sponsor. The study monitor will ensure that any outstanding data

clarification issues and queries are resolved, and that all study records at the study site are complete.

In accordance with applicable regulatory requirements, the Sponsor will promptly inform the competent regulatory authorities of the termination and its reason(s), and the investigator or Sponsor will promptly inform the Independent Ethics Committee (IEC)/Institutional Review Board (IRB).

3.7 STUDY MONITORING PROCEDURES

3.7.1 Independent Data and Safety Monitoring Committee

The IDSMC is an independent advisory body that monitors participant safety, data quality and progress of the clinical trial. The IDSMC charter will outline the roles and responsibilities of the committee and guide its operations and frequency of meetings. The IDSMC will consist of individuals external to the Sponsor who have relevant clinical trial expertise and experience in safety assessment; international members of the IDSMC include a pediatric neurologist, pediatric cardiologist, general pediatrician, pediatric epileptologist, and a statistician.

At regularly defined intervals, the IDSMC will convene to review and monitor study progress, AEs and serious adverse events (SAEs), other measures of safety such as ECGs or ECHOs, and efficacy data as dictated by the charter.

The IDSMC will:

- Be responsible for providing recommendations to the Sponsor surrounding study conduct matters that affect safety.
- Review safety data at ad hoc time points and identify if significant safety concerns arise during the study.
- Review PK data and any other data that may affect subject continuation.
- Make recommendations regarding the continuation, suspension, or termination of the study.
- Be informed of the dose selection for Cohort 2.

3.7.2 International Pediatric Cardiac Advisory Board (IPCAB)

The International Pediatric Cardiac Advisory Board (IPCAB) is an advisory body to the Sponsor that monitors cardiac safety of the ZX008 clinical trials and provides advice to the IDSMC. The IPCAB charter outlines the roles and responsibilities of the committee and guide its operations, and reviews individual subject cases. The IPCAB consists of individuals external to the Sponsor who have relevant experience in cardiology, pediatric cardiology, and echocardiography. The IPCAB will advise the Sponsor and the IDSMC on the cardiac safety

monitoring plan, including alert criteria and decision pathway for subject management relative to cardiac safety in the clinical studies of ZX008.

All ECHO examinations performed throughout the trial will be sent to an experienced pediatric cardiologist central reader (Biomedical Systems, Inc.); during the double-blind phase of the study, the central reader will be blinded as to each subject's treatment. If the central reader classifies a subject as having met a pre-defined threshold value indicative of potential cardiac valvulopathy or pulmonary hypertension, or any other unexpected cardiac AE, the case will then be sent for secondary adjudication by one or more members of the IPCAB according to the procedures outlined in the IPCAB manual. In addition, members of the IPCAB will perform audits of ECHOs deemed normal by the central cardiac reader.

4. SELECTION OF STUDY POPULATION

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Before evaluating these criteria and deciding on the eligibility of subjects to participate in the study, it is important that the investigator is familiar with the safety profile of ZX008 by referring to the Investigator's Brochure (2016), as supplied by the Sponsor.

4.1 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to be enrolled into the study:

1. Subject is male or non-pregnant, non-lactating female, age 2 to 18 years, inclusive as of the day of the Screening Visit. 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 (see Section 4.4), which includes abstinence, while being treated on this study and for 90 days after the dose of study drug.
2. Subject must have documented medical history to support a clinical diagnosis of Dravet syndrome, where convulsive seizures are not completely controlled by current antiepileptic drugs.
3. Subjects must meet all of the following 5 criteria:
    a. Onset of seizures in the first year of life in an otherwise healthy infant.
    b. A history of seizures that are either generalized tonic-clonic or unilateral clonic or bilateral clonic, and are prolonged.
    c. Initial development is normal.
    d. History of normal brain magnetic resonance imaging (MRI) without cortical brain malformation.
    e. Lack of alternative diagnosis.

4. Subjects must meet at least one of the following 3 criteria:
    a. Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal has developed after the first seizure type.
    b. Prolonged exposure to warm temperatures induces seizures and/or seizures are associated with fevers due to illness or vaccines, hot baths, high levels of activity and sudden temperature changes and/or seizures are induced by strong natural and/or fluorescent lighting, as well as certain visual patterns.
    c. Genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis.)
5. Subject must have had ≥ 4 convulsive seizures (tonic-clonic, tonic, clonic) per 4-week period for 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes (**Cohort 2 only**).
6. All medications or interventions for epilepsy (including ketogenic diet [KD] and vagal nerve stimulation [VNS]) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
7. Subject must be receiving a therapeutically relevant and stable dose of CLB, VP, and STP for at least 4 weeks prior to screening and are expected to remain stable throughout the study (**Cohort 2 only**). (In some cases, subjects who are contraindicated for VPA or CLB may be enrolled in Cohort 2. Subjects in these cases must be receiving a therapeutically relevant and stable dose of STP and VPA [if contraindicated for CLB] or STP and CLB [if contraindicated for VPA]. Each subject must be reviewed with the Medical Monitor and sponsor before initiating screening. The decision to allow enrollment of these subjects is at the sole discretion of the sponsor.)
8. Subject must be receiving a stable dose of CLB and VPA, administered BID, to be eligible for Dose Regimen 1 and 2 or subject must be receiving a stable dose of CLB, VPA, and STP, administered BID, to be eligible for Dose Regimen 3 (**Cohort 1 only**).
9. Subject agrees to provide a buccal swab for CYP2D6 (cytochrome P450 2D6) genotype/phenotype.
10. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
11. Subject has provided assent in accordance with IRB/IEC requirements, if capable.
12. Subject's parent/caregiver is willing and able to be compliant with all study requirements and visit schedule. Subject's parent/caregiver must also be willing and able to be compliant with diary completion and study drug accountability.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following exclusion criteria must not be enrolled into the study:

1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication.
2. Subject has pulmonary arterial hypertension.
3. Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke.
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. Subject has a current or past history of glaucoma.
6. Subject has moderate or severe hepatic impairment.
   a. Asymptomatic subjects with mild hepatic impairment (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] < 2x the upper limit of normal (ULN) and no elevations of gamma-glutamyltransferase [GGT], alkaline phosphatase, or total bilirubin indicative of more than mild hepatic impairment) 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 (**Cohort 1 only**).
   b. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x the 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 (**Cohort 2 only**).
7. 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; triptans, atomoxetine, or other centrally-acting noradrenergic agonist; or cyproheptadine (see Appendix 1). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)
8. Subject is currently receiving or has received STP in the past 21 days prior to Screening (**only for Cohort 1 subjects allocated to Dose Regimen 1 or 2**).
9. Subject is currently taking carbamazepine, oxcarbazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy.
10. Subject is unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges, and their juices beginning with the Baseline Period and throughout the study.
11. Subject has positive result on urine THC Panel or whole blood CBD at the Screening Visit.
12. Subject has participated in another clinical trial within the past 30 days.
13. Subject is currently receiving an investigational product.

14. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
15. 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.

4.3 RANDOMIZATION INCLUSION CRITERIA – COHORT 2

Subjects must meet all of the inclusion criteria above plus the following criteria, to be randomized (Cohort 2):

1. Subject has been approved for study inclusion by the Epilepsy Study Consortium.
2. Subject does not have a cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination, including but not limited to trace mitral or aortic valve regurgitation or signs of pulmonary hypertension, and is approved for entry by the central cardiac reader.
3. Subject demonstrates a stable baseline with ≥ 6 convulsive seizures during the 6-week Baseline Period, with a minimum of 2 in the first 3 weeks and 2 in the second three weeks.
4. Subject's parent/caregiver has been compliant with diary completion during the Baseline Period, in the opinion of the investigator (eg, at least 90% compliant).

4.4 SUBJECTS OF REPRODUCTIVE POTENTIAL

Male subjects who are sexually active with a partner of child-bearing potential must use, with their partner, a condom plus an approved method of highly acceptable contraception from the time of informed consent until 90 days after last dose of study drug.

The following methods are acceptable:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable intrauterine device
  - intrauterine hormone-releasing system
- Surgical sterilization (vasectomy or bilateral tubal occlusion)

Female subjects who are not of child-bearing potential do not need to use any methods of contraception. A woman is considered of childbearing potential, unless they are at least 2 years post-menopausal or permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Female subjects who are sexually active and are of child-bearing potential must use, with their partner, an approved method of highly effective contraception from the time of informed consent until 90 days after the last dose of study drug.

The following methods are acceptable:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation and a barrier method (ie, condom for male partner):
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation and a barrier method (ie, condom for male partner)
  - oral
  - injectable
  - implantable intrauterine device
  - intrauterine hormone-releasing system
- Surgical sterilization (vasectomy or bilateral tubal occlusion)

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.

4.4.1 Sperm and Egg Donation

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.

4.4.2 Pregnancy

Subjects will be instructed that if they/their partner become pregnant during the study this should be reported to the investigator. 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 subject 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.

4.5 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

While subjects are encouraged to complete all study evaluations, subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make a genuine effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the electronic case report form (eCRF). All subjects who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical site should be collected at the time of premature discontinuation or at the scheduled discharge.

For subjects who are lost to follow-up (ie, those subjects whose status is unclear because they failed to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents the steps taken to contact the subject (eg, dates of telephone calls, registered letters).

Subjects must be discontinued from the study for the following reasons, if deemed appropriate by the Sponsor or investigator:

1. Development of signs or symptoms indicative of cardiac valvulopathy or regurgitation (mitral, aortic, tricuspid, pulmonary valves), or pulmonary hypertension for which IDSMC, in consultation with the IPCAB, the central cardiac reader, and the investigator believe the benefit of continued participation does not outweigh the risk.

2. Subject is found to have entered the clinical investigation in violation of the protocol.

3. Subject requires or starts using the use of an unacceptable or contraindicated concomitant medication.

4. Subject's condition changes after entering the clinical investigation so that the subject no longer meets the inclusion criteria or develops any of the exclusion criteria.

5. Subject is noncompliant with procedures set forth in the protocol in an ongoing or repeated manner.

6. Subject experiences an AE that warrants withdrawal from the clinical investigation.

7. Clinically significant worsening of seizures, judged by investigator or subject/caregiver such that treatment outside of the protocol and other than ZX008 is assumed to be in the subject's best interest. Frequent or increased use of rescue medication may be considered indicative of worsening.

8. An "actual suicide attempt" as classified by the Columbia-Suicide Severity Rating Scale (C-SSRS).

9. It is the investigator's opinion that it is not in the subject's best interest to continue in the study.

10. Subject is found to be pregnant while on study.

Discontinuation decisions will be made at each participating site by the site investigator, except that discontinuations due to development of cardiovascular or cardiopulmonary complications are to be made by the IDSMC with input from the IPCAB and the investigator.

If feasible, the process of discontinuation should be discussed with the Medical Monitor. The decisions regarding the discontinuation of the investigational therapy, whether the study medication should be stopped immediately or tapered should be discussed with the Medical Monitor, but final decisions about the process will remain at the discretion of the site principal investigator.

Subjects who are discontinued from the clinical investigation (Cohort 2) for any reason will not be replaced.

Subjects may withdraw their consent to participate in the study at any time without having to justify the reason for doing so. The decision to withdraw consent and discontinue participation in the study will not prejudice the subject's future medical treatment in any way. Subjects must be discontinued from receiving ZX008 and/or participating in any further study procedures under the following circumstances:

- The subject or the subject's legally authorized representative wishes to discontinue participation in the study.

- The investigator advises that the subject's safety or well-being could be compromised by further participation in the study.

- The Sponsor requests that a subject discontinues participation in the study (eg, due to suspicion of fraud, multiple enrollments in clinical studies, lack of compliance, etc).

The IDSMC may request that the study be terminated after review of the safety information at any time during the study. The IDSMC will review the data for the development of heart valve disease and pulmonary hypertension as they occur on a case-by-case basis and at regular meetings.

In the event that the study is terminated prematurely then the procedure for termination should be followed as described in Section 3.6. Concern for the interests of the subject will always prevail over the interests of the study.

The reason for, and date of discontinuation from participation in the study must be recorded in detail in the eCRF and in the subject's medical records (eg, AEs, lack of compliance, lost to follow-up, etc). If possible, the subject/subject's legal representative should confirm his decision in writing.

The investigator will attempt to complete all procedures usually required at the end of the study at the time when the subject's participation in the study is discontinued or as close as possible to that time. Specific procedures required are described in Section 6.1.5, Section 6.2.5.10, and Section 6.2.5.11. As far as possible, a complete final examination must be performed on all subjects who do not complete the study according to the study protocol.

Data collected until the time a subject discontinues participation in the study will be handled in the same manner as data for subjects completing the study. Where possible, further information will be collected if any AEs are experienced by a subject after discontinuing participation in the study.

4.6 TERMINATION OF THE CLINICAL STUDY

If the investigator, the Sponsor, the Medical Monitor, or the IDSMC becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated. The clinical study may be terminated at the Sponsor's discretion at any time also in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study.
- Failure to enroll subjects at the required rate.
- A decision of the Sponsor to suspend or discontinue development of ZX008.

4.7 REPLACEMENT OF SUBJECTS

Approximately 25 subjects will be screened for Cohort 1 to ensure that subjects enter the study and complete all PK assessments; participants who discontinue prior to completion of all study-related procedures may be replaced. Approximately 115 subjects will be screened for Cohort 2 to randomize approximately 90 subjects into the T + M Period; randomized subjects will not be replaced.

4.8 ELIGIBILITY FOR EXTENSION TRIAL

Subjects from Cohort 1 who complete the PK portion of this study or subjects from Cohort 2 who complete the 12-week Maintenance Period of this study will be eligible to enrol in a planned, separate, open-label extension trial of ZX008 if they meet Inclusion/Exclusion criteria for that study are deemed eligible for continued participation in a trial of fenfluramine. Cohort 1 subjects must have tolerated the IMP and the Investigator also must feel that the subject would benefit from long term therapy with ZX008 for other multiple seizure types, eg, pattern sensitivity, photosensitivity, severe absences, nocturnal seizures, severe myoclonus which are not managed with current therapy. Subjects from Cohort 1 may not enter the separate, open-label extension trial until the dose for Cohort 2 has been selected.

Those subjects who do not complete the PK phase or the 12-week Maintenance Period of the study may, on a case-by-case basis, be eligible for entrance into the separate open-label extension trial after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a ZX008 trial. The decision whether to permit open-label extension trial participation resides solely with the Sponsor, who may consult with the site investigator, the IPCAB and/or the IDSMC.

5. INVESTIGATIONAL MEDICINAL PRODUCT INFORMATION

ZX008/matching placebo will be administered in the current study. A brief description of the ZX008 product is provided below (Table 4).

Table 4. Investigational Medicinal Product – ZX008

	Study Product
Substance Code	ZX008
Active Substance (INN)	Fenfluramine hydrochloride
Trade Name	Not applicable
Formulation (including dosage form and strength)	Solution 1.25, 2.5, and 5 mg/mL
Route/Mode of Administration	Oral
Manufacturer	PCI Pharma Services on behalf of Zogenix International Limited

The IMP(s) will be administered by the oral route.

Background medications (Cohort 1): On the day prior to dosing (Day -1) the parents/caregivers will be reminded to bring the subject's usual epilepsy medications (CLB + VPA or CLB + VPA + STP) and any other epilepsy medications the patient may be taking, to the CRU on the day of dosing (Day 1) for AM and PM administration, as applicable.

5.1 IDENTITY OF INVESTIGATIONAL MEDICINAL PRODUCT

ZX008 drug product is an oral aqueous solution of fenfluramine hydrochloride buffered to pH 5 and provided in concentrations of 1.25 mg/mL, 2.5 mg/mL, and 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 colored, and will contain preservatives and a thickening agent. The product is sugar free and is intended to be compatible with a KD.

The formulation will be provided in bottles with tamper-evident, child-resistant caps. The clinical trials material will be supplied in 1 bottle size with nominal fill volume of 120 mL. Matching placebo for Cohort 2 also will be provided. Doses to be studied include 0.2 mg/kg and 0.4 mg/kg for Cohort 1 during the PK portion of the study; subjects will receive ZX008 at a fixed dose of 0.2 mg/kg/day in the Cohort 1 transition period. Dosing for Cohort 2 was informed based on evaluation of Cohort 1 and Study ZX008-1505 data, and assigned to be 0.5 mg/kg/day and no more than 20 mg/day.

If the parent/caregiver for Cohort 2 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. **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.

5.1.1 Packaging and Labeling

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.

5.2 DESCRIPTION OF REFERENCE TREATMENT, COMPARATOR, AND/OR PLACEBO

Placebo solution is identical in aspect and composition to ZX008 and is composed of identical ingredients used in the ZX008 formulation, except that it does not contain the active ingredient, fenfluramine hydrochloride.

No comparators or reference treatments will be used.

5.2.1 Packaging and Labeling

Placebo solution will be packaged in an identical manner to ZX008. The matching placebo product will be packaged and labeled according to current ICH, GMP, and 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.

5.3 SHIPMENT AND STORAGE

IMP will be supplied to the study sites 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.

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 with excursions of 5-30°C permitted; do not 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.

5.4 IMP ACCOUNTABILITY

The investigator or delegate will confirm receipt of all shipments of the IMP in writing using the receipt form(s) provided by the Sponsor or vendor.

For both cohorts, assignment of IMP to the subject will be handled through an interactive voice randomization (IVR) or Interactive Web Response (IWR) platform. The investigator or delegate will be required to register the subject through IVR/IWR and all study medication will be assigned to the subject through the IVR/IWR. The IVR/IWR will also maintain a log of all received and dispensed medication.

All supplies must be accounted for throughout the study using the study drug accountability form. At the end of the study, the dated and signed (by the investigator or delegate, eg, pharmacist) original drug accountability form must be retained at the study site as verification of final drug accountability.

Records for the delivery of the IMP to the study site, the inventory at the study site, the use by each subject (use by subject will be documented in the subject diary), and the destruction or return of the IMP to the Sponsor must be maintained by the investigator (or delegate). The records will include dates, quantities, batch numbers, and unique code numbers assigned to the IMP and to the subjects. The investigator must maintain records documenting that subjects were provided with the doses of the IMP specified in this study protocol. Furthermore, the investigator must reconcile all IMPs received from the Sponsor. The investigator must provide reasons for any discrepancies in drug accountability. Forms will be provided by the Sponsor to ensure standardized and complete drug accountability.

5.5 TREATMENT ADMINISTRATION

5.5.1 Cohort 1: Randomization

For Cohort 1, participants in Regimen 1 and Regimen 2 will be randomized to open-label treatment, stratified by age. A randomization schedule will be produced for these two regimens and provided to the sites. Subjects who enter the study on CLB + VPA will be randomized to treatment with a single dose of ZX008 0.2 mg/kg added to their usual dose of CLB + VPA (Regimen 1) or a single dose of ZX008 0.4 mg/kg added to their usual dose of CLB + VPA (Regimen 2). Randomization will be stratified by age ensure that both Regimens 1 and 2 have at least 2 subjects < 6 years old and at least 2 subjects ≥ 6 years old. Subjects who enter the study on STP + CLB + VPA will be assigned to Regimen 3 (ZX008 0.2 mg/kg + CLB + VPA + STP).

5.5.2 Cohort 2: Randomization

For subjects who enter Cohort 2, upon completion of the Baseline Period, subjects who qualify for the study will be randomized (1:1) in a double-blind manner to receive either treatment with ZX008 (0.5 mg/kg/day, 20 mg/day maximum) or placebo. The randomization will be stratified by age (< 6 years, ≥ 6 years) to ensure balance across treatment arms, and at least 40% of subjects will be in each age group. Subjects will be assigned a randomization number by the

IVR/IWR system upon confirmation that the subject qualifies for enrollment in the Titration Period. Once a randomization number is assigned to a subject, the site will record the subject's initials and identification number on the corresponding study drug bottles. Each bottle will contain the assigned treatment (ZX008 or placebo). ZX008 and placebo will be identical, thus rendering the study drug and placebo indistinguishable. For each IMP bottle and randomization number assigned, the following information will be recorded on the drug accountability form: subject initials, unique bottle number, date each bottle is assigned, and drug used and unused during the study.

5.5.3 Cohort 2: Titration Period

The investigator (or delegate) will dispense IMP only to subjects included in this study following the procedures set out in this study protocol.

Study medication will be administered as equal doses BID in the morning and in the evening approximately 12 hours apart, with food. 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. Administration of the IMP will be based on the randomized dose and subject's weight at Visit 3 (Study Day -1). At Visit 8 (Day 50), if the subject's weight has changed ±25% of the weight at Day-1, the IMP dose will be recalculated. Subjects will be dosed using the oral dosing syringe provided.

The assigned 0.5 mg/kg/day (maximum 20 mg/day) dose for Cohort 2 was informed based on PK and safety data from Cohort 1, where single doses of 0.2 and 0.4 mg/kg together with data from Study ZX008-1505 were evaluated. In order to maximize tolerability, the dose for each subject will be titrated to 0.5 mg/kg/day. All subjects will start with a dose of ZX008 0.2 mg/kg/day (or placebo equivalent), administered in divided doses BID (maximum 20 mg/day) on Study Days 1-7. The dose will be increased to ZX008 0.4 mg/kg/day (or placebo equivalent) administered in divided doses BID (maximum 20 mg/day) on Study Days 8-14. The dose of ZX008 will be increased to 0.5 mg/kg/day (or placebo equivalent) administered in divided doses BID (maximum: 20 mg/day) on Study Days 15-21. The titration algorithm is shown in Table 5. See Section 5.6 for more information about the volume of ZX008 or placebo to be administered.

Table 5. Titration Algorithm

Randomized Dose	Titration Step 1 Study Days 1-7	Titration Step 2 Study Days 8-14	Titration Step 3 Study Days 15-21
ZX008 0.5 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.5 mg/kg/day
Placebo	Placebo	Placebo	Placebo
Note: maximum daily dose of ZX008 is 20 mg; the dosing regimen for all doses is BID			

5.5.4 Cohort 2: Maintenance Period

After completion of the Titration Period, subjects will enter the Maintenance Period and continue to receive the randomized 0.5 mg/kg/day (maximum 20 mg/day) dose of ZX008 or placebo and be treated for an additional 12 weeks on stable dosage. Study medication will continue to be administered BID in the morning and in the evening, approximately 12 hours apart, with food. 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.

5.5.5 Cohort 2: Taper Period

Subjects who complete all of the Maintenance Period and will not be continuing into the open-label extension trial, and subjects who discontinue from the study early, will be tapered off of study medication over 8 days and will receive no study drug during the final 6 days of the taper period. Study drug administration will not be resumed after completion of the taper period. The taper algorithm is shown in Table 6.

Table 6. Taper Algorithm

Randomized Dose	Taper Step 1 Days 1-4 after study completion or early termination	Taper Step 2 Days 5-8 after study completion or early termination	Taper Step 3 Days 9-14 after study completion or early termination
ZX008 0.5 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day	No study drug administration
Placebo	Placebo	Placebo	No study drug administration
Note: maximum daily dose of ZX008 is 20 mg			

Study medication will continue to be administered as equal doses BID in the morning and in the evening approximately 12 hours apart, with food. 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. IMP will be administered using the oral dosing syringe provided.

5.5.6 Cohort 1: Transition Period

For Cohort 1, participants who choose to enter the open-label extension trial will begin a transition period on Study Day 15. All subjects will receive a dose of ZX008 0.2 mg/kg/day added to their usual AED regimen. Study medication will be administered as equal doses BID in the morning and in the evening approximately 12 hours apart, with food. 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. Study medication will be administered using the oral dosing syringe provided. This dose of ZX008 0.2 mg/kg/day will continue until the dose for Cohort 2 has been chosen and the subject is entered into the separate open-label extension trial.

5.5.7 Cohort 2: Transition Period

Subjects who complete the Maintenance Period and will be continuing into the open-label extension trial will be transitioned from double-blind study medication to open-label ZX008 (depicted in Table 7). Study medication will be administered as equal doses BID in the morning and in the evening approximately 12 hours apart, with food. 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. Study medication will be administered using the oral dosing syringe provided.

This transition is required in order to maintain the blind. All subjects entering the open-label extension trial will be transitioned from their blinded daily dose (placebo, or 0.5 mg/kg/day [maximum 20 mg/day] dose of ZX008) to the 0.2 mg/kg/day ZX008 dose during the interval between Visits 12 and 13, without breaking the blind. Subjects in the ZX008 arm will transition to 0.4 mg/kg/day dose on Days 1-7, and then transition to a dose of 0.2 mg/kg/day on Days 8-14 during the transition period. Subjects in the placebo arm will have a titration step from placebo to 0.2 mg/kg/day and then will commence taking study medication as per the open-label extension trial (0.2 mg/kg/day). All subjects will receive ZX008 0.2 mg/kg/day for the last transition step in their respective dose group. A new bottle of IMP will be started by the subject at each level of the transition step. See Section 5.6 for more information about the volume of ZX008 or placebo to be administered.

Table 7. Transition Algorithm

Randomized Dose Selected for Cohort 2	Step 1 Days 1-7 after study completion	Step 2 Days 8-14 after study completion
ZX008 0.5 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
Placebo	Placebo	ZX008 0.2 mg/kg/day
Note: maximum daily dose of ZX008 is 20 mg		

5.6 BLINDING (COHORT 2)

At the end of the Baseline Period, subjects who qualify to enter the double-blind portion of the study will be randomized to receive ZX008 (0.5 mg/kg/day, maximum dose 20 mg/day), or placebo and assigned a randomization number by the IVR/IWR system. Once a randomization number is assigned to a subject, the site will record the subject's initials on the corresponding study drug labels. Each bottle will contain the assigned treatment (ZX008 or placebo) and the

ZX008 and placebo solutions will be identical.

The IVR/IWR system will instruct site personnel to the volume of oral solution to be administered based on that subject's weight. (Dose will be recalculated by the system once at the midpoint of the study.) During the Titration, Maintenance, Taper/Transition Periods, the subjects and study personnel (investigators, clinical staff, personnel involved in data collection and analysis, the Medical Monitor, and the Sponsor) will be blinded to the treatment allocation. If an investigator feels the blind should be broken, he/she should endeavor to discuss with the Medical Monitor or Sponsor's Medical Representative in consideration of the nature of the emergency and the availability of the Medical Monitor or Sponsor's Medical Representative that the blind should only be broken in the event the knowledge of whether the subject is on active study medication versus placebo is needed to determine course of medical treatment for an AE or SAE; that the subject will be discontinued from the clinical trial upon breaking of the blind; and that the decision whether the subject can enter the separate open-label extension trial will rest with the Sponsor if the subject exited Study ZX008-1504 prior to completion.

5.7 PRIOR AND CONCOMITANT MEDICATIONS

All medications taken by a subject during the Screening and Baseline Seizure Assessment Periods are regarded as prior therapy and must be documented in the eCRF. Significant medications (eg, antibiotics) taken within 30 days prior to the Screening visit should also be captured. All prior and concomitant AEDs will be collected in the CRF.

All medications taken by a subject after the first administration of IMP are regarded as concomitant medications and must be documented in the eCRF, including over-the-counter medication, herbal, and vitamin/supplement preparations. Subjects are required to take at least one concomitant AED during the study. All subjects will continue to receive their existing AED(s) with the same doses throughout the study. Every effort should be made to ensure that the regimen of existing medications remains stable during the study; any changes must be discussed with the Sponsor prior to implementation. If a change is necessary to manage an AE, this must be discussed with the Sponsor as soon as possible after implementation if not before implementation. Non-study medications and therapies that are considered necessary for the subject's welfare and will not interfere with the response to the study medication may be given at the discretion of the investigator, informing the Medical Monitor as soon as possible.

It should be noted for any subject receiving hypoglycemic agents, the investigator should consider diabetic medication changes in the setting of weight loss and hypoglycemia.

5.7.1 Vagal Nerve Stimulation

Subjects receiving treatment with a VNS may be included in the study as long as the VNS has been in place for at least 6 months prior to entry into the study, the VNS battery is not due for

replacement during the study, and stimulation parameters have been kept constant for 4 weeks prior to screening and must remain so throughout the study. The subject's use of VNS will be recorded in the eCRF.

5.7.2 Ketogenic Diet

Adherence to the KD, or a modified version of KD, is permitted during the study if the dietary habits were initiated more than 4 weeks prior to Screening and remain stable throughout the study. The subject's use of KD will be recorded in the eCRF.

5.7.3 Rescue Medication for Seizures

The subject's usual or prescribed regimen and frequency of rescue therapy for seizures should be entered into the prior and or concomitant medications sections of the eCRF.

Use of rescue medication is permitted during the study and should be recorded on the eCRF (day, medication[s], dose[s]) and in the diary (day, timeframe associated with seizure episodes). Repeated administrations within the same episode should be recorded separately.

5.7.4 Prohibited Concomitant medications and Food

Alcohol in all forms (wine, beer, liquors) and amounts is prohibited during the study. The following concomitant medications/foods are prohibited during the clinical trial:

- AEDs: Phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, retigabine/ezogabine, or phenobarbital
- Felbamate is prohibited as a concomitant medication unless the subject has been on felbamate for at least 18 months prior to screening, has stable liver function and hematology laboratory tests, and the dose is expected to remain constant throughout the study.
- Any centrally-acting medication with clinically appreciable amount of serotonin agonist or antagonist activity, including imipramine, monoamine oxidase inhibitors, serotonin-reuptake inhibitors or mixed norepinephrine/serotonin reuptake inhibitors, vortioxetine, cyproheptadine, or any of the triptans (for migraine).
- Drugs that increase cardiovascular risk: atomoxetine and those with noradrenergic reuptake properties
- Drugs intended to facilitate weight loss
- Other: any form of marijuana, THC and derivatives (including Epidiolex®)

- A list of medications/foods that are to be avoided as ongoing medications or for chronic use if initiated during the study from the time of signing the informed consent form (ICF) until the end-of-study visit (or early termination) is provided in Appendix 1. If medical necessity requires short-term use of one or more of these medications during the course of the study, please contact the Medical Monitor for approval. The use of diazepam or midazolam as rescue medication does not require Medical Monitor approval prior to use.

5.8 TREATMENT COMPLIANCE

Each subject or parent/caregiver will record the dose, dosing frequency and IMP consumption in the subject's diary. Subjects will bring their used, partially used, and unused IMP to every study visit. Treatment compliance will be monitored by measuring the volume of IMP in these bottles and comparing to the dispensation log and diary records.

6. VISIT SCHEDULE

For both Cohorts, study procedures will be conducted according to the Schedule of Assessments in Table 1 and Table 2. Time windows for transition period assessments in Cohort 1 and all assessments in Cohort 2 are detailed in Table 8 and Table 9, respectively. Note that for Cohort 1 the screening period may be extended to ensure all screening results are reviewed for eligibility prior to dosing.

Table 8. Cohort 1: Time Windows for Assessments During the Transition Period

Transition Period Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 6 (Phone; Day 29)	± 3 days
Visit 7 (Clinic; Day 43)	± 4 days
Visit 8 (Phone: Day 57)	± 3 days
Visit 9 (Clinic; Day 71)	± 4 days
Visit 10 (Phone: Day 85)	± 3 days
Visit 11 (Clinic; Day 99)	± 4 days
Visit 12 (Phone: Day 113)	± 3 days
Visit 13 (Clinic; Day 127)	± 4 days
Visit 14 (Phone: Day 141)	± 3 days
Visit 15 (Clinic: Day 155)	± 4 days
Visit 16 (Phone: Day 169)	± 3 days
Visit 17 (Clinic: Day 183)	± 4 days
Visits 18 and 19 (ECHO clinic; 3-6 months after last dose)	± 30 days
Blood collection for AED concentration	Prior to morning dose of AED medication

AED=antiepileptic drug (s); ECHO=echocardiogram

Table 9. Cohort 2: Time Windows for Assessments

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Clinic; Day -43 to -42, or -42 to -41: Screening)	Not applicable
Visit 2 (Phone; Day -21)	± 3 days
Visit 3 (Clinic; Day -1; Randomization)	+ 4 days
Visit 4 (Clinic: Day 8)	+ 4 days
Visit 5 (Clinic; Day 15)	+ 4 days
Visit 6 (Clinic; Day 22)	+ 4 days
Visit 7 (Phone: Day 36)	± 4 days
Visit 8 (Clinic; Day 50)	± 4 days
Visit 9 (Phone: Day 64)	± 4 days
Visit 10 (Clinic; Day 78)	± 4 days
Visit 11 (Phone: Day 92)	± 4 days
Visit 12 (Clinic: Day 106)	± 4 days
Visit 13 (Clinic; Day 120; post-dosing)	± 4 days
Visit 14 (ECHO clinic; 3-6 months after last dose)	± 30 days
Blood collection for ZX008 PK	± 15 minutes
Blood collection for AED concentration	Prior to morning dose of AED medication

AED=antiepileptic drug (s); ECHO=echocardiogram; PK = pharmacokinetics

6.1 COHORT 1: STUDY PROCEDURES

6.1.1 Screening (Up to 14 days prior to dosing)

Screening is the predetermined series of procedures with which each investigator selects an appropriate and representative sample of subjects for enrollment into the study. Subjects will attend the clinical unit for a screening visit up to 14 days prior to dosing. The screening period may be extended to ensure all screening results are reviewed for eligibility prior to dosing. Select screening data will be entered into the eCRF.

Written informed parental or guardian consent and assent of minors (if the subject is capable of providing assent) must be obtained before a subject can start any of the screening procedures. The procedure(s) for obtaining written informed consent and assent of minor (if the subject is capable of providing assent) are described in Section 11.2.

The following procedures will be performed during the Screening visit, which may be split into two visits:

- Obtain written informed consent for the study
- Review inclusion and exclusion criteria
- Record demographic information
- Record medical, neurological, and epilepsy history

- Record current epilepsy status (number/type/duration seizures per month)
- Record prior medications
- Complete physical examination, including height, weight, and calculation of BMI
- Complete neurological examination
- 12-lead electrocardiogram
- Doppler ECHO
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, hematology, urinalysis, tests of growth and precocious puberty, coagulation)
- Urine THC panel
- Whole blood CBD
- Obtain blood sample for epilepsy genotype panel
- Obtain buccal swab for CYP2D6 genotype/phenotype characterization.

Only eligible subjects as specified by the inclusion and exclusion criteria with an independently confirmed diagnosis of Dravet syndrome by the Epilepsy Study Consortium will be enrolled into the study.

After enrollment into the study, each subject will be issued a "Subject Card" containing information about the subject's participation in the study. The subject or parent/caregiver will be advised to retain this card on his person for the entire duration of the study so that the investigator or the Sponsor can be contacted in case of emergency.

If a subject does not meet all inclusion/exclusion criteria at the time of the Screening Visit, the subject may be rescreened later to determine eligibility, upon approval from the Medical Monitor.

6.1.2 STUDY DAY -1

On the day prior to dosing, subjects will return to the CRU for an outpatient visit. The identity of the subjects will be confirmed at admission and at pre-dose. In addition, the ongoing eligibility of subjects will be re-assessed including: review of inclusion and exclusion criteria, any updates to screening medical history, symptom-derived physical exam (at the investigator's discretion), weight and BMI, urine pregnancy test for subjects of childbearing potential, vital signs and clinical labs, whole blood CBD and urine THC will be collected. These are baseline lab assessments and results will not be available prior to dosing. Adverse events and concomitant medications will be recorded. Subjects will be discharged from the CRU or permitted to stay overnight, as needed. Following dinner and a light evening snack, subjects will be required to fast overnight (for at least 10 hours).

6.1.3 STUDY DAY 1

On the morning of the next day, Study Day 1, subjects will return to the CRU between 6:00 AM and 7:00 AM. Prior to dosing, the identity of the subject will be reconfirmed, vital signs will be assessed. Subjects will then be provided with a light, low fat breakfast. Following breakfast, subjects will continue to fast for approximately 4 hours post-dose at which time lunch will be provided. Water will not be restricted. One hour or less prior to dosing, a blood sample for PK assessment will be obtained from all subjects (blood samples will be obtained via indwelling catheter). Subjects will then take their usual epilepsy medications. Based on the treatment allocation, each subject will then receive their assigned dose of study medication (ZX008).

With administration of tablets/capsules, subjects will be given water immediately following oral administration. When subjects are administered an oral solution, the dosing vessel will be rinsed twice with water and the subjects will consume the rinse solutions immediately after dosing. The exact time of dosing will be decided based on logistics and will be documented in the source workbook. During dosing, subjects will be observed by study staff to ensure the tablet/capsule/solution has been swallowed. Mouth and hand checks will be conducted after dosing to ensure that all medications have been ingested.

Four mL blood samples for PK assessment will be collected at 2 hours, 4 hours, 8 hours, and 12 hours post-dose, after vital signs are performed. Vital signs will be performed at 2 and 8 hours post-dose. An evening meal will be provided at approximately 9 hours post-dose and an evening snack at approximately 12 hours post-dose. Approximately 12 hours post-dose, after the 12-hour PK sample has been collected, subjects will take the PM dose of their usual epilepsy medications. Reported or observed adverse events and any concomitant medications will be recorded, and the subject will be discharged from the CRU or permitted to stay overnight, if required.

6.1.4 STUDY DAY 2

Twenty-four to 36 hours post-dose, subjects will return to the CRU for a final PK sample. A 4-mL blood sample for PK assessment will be collected, and the time recorded, after vital signs are performed. Reported or observed adverse events and any concomitant medications will be recorded. A seizure diary will be provided so that parents can record any seizure activity that occurs between the Study Day 2 and the Study Day 15 visit.

6.1.5 STUDY DAY 15

All subjects will return to the CRU on Day 15. The following will be recorded/performed:

- Review current seizure activity (number/type/duration) from diary since previous visit

- Abbreviated physical examination, including height and weight, and calculation of BMI
- Abbreviated neurological examination
- Urine pregnancy test for females of child-bearing potential
- Record current epilepsy status (number/type/duration seizures per month)
- Tanner Staging for subjects > 7 years of age (Appendix 5)
- Collect plasma sample for background AED PK evaluation prior to the morning dose of study medication(s)
- Collect and review diary with parent/caregiver
- Dispense diary
- AEs
- Adverse events of special interest (AESI)
- Concomitant medications
- Administer healthcare utilization questions
- C-SSRS Children's Baseline/Screening Assessment (Appendix 2)
- PedsQL Generic Core Scale
- BRIEF (Appendix 3)
- QOLCE for subjects ≥5 years of age (Appendix 4)
- Parent/Caregiver quality of life (QoL) using the EQ-5D-5L scale (Appendix 7)
- PedsQL Family Impact Module (Appendix 6)
- Sleep quality and mealtime behavior questions
- Karolinska Sleepiness Scale
- Dispense study medication

Subjects who will enter the open-label extension trial will be transitioned to ZX008 (0.2 mg/kg/day), and will be dispensed study medication to begin taking the next morning in accordance with the study protocol; see Section 6.1.6.

6.1.6 Transition Period

Subjects who complete Day 15 activities will enter a transition period where they will receive open-label ZX008 (0.2 mg/kg/day). Subjects will have every-2-week phone visits and will attend every-4-week clinic visits until the dose for Cohort 2 has been selected and the open-label extension trial is open for enrollment. The number of phone and clinic visits will be determined based on the selection of the dose for Cohort 2 and the availability of the open-label extension trial not to exceed 24 weeks.

6.1.6.1 Phone Visits 6, 8, 10, 12, 14, and 16 (Study Days 29, 57, 85, 113, 141, and 169)

Site personnel will contact the subject via telephone on Study Days 29, 57, 85, 113, 141, and 169 and record the following:

- AEs
- AESI
- Concomitant medications
- Healthcare utilization questions

In addition, site personnel will review study medication dosing procedure and the diary entries with the parent/caregiver.

6.1.6.2 Clinic Visits 7, 9, 11, 13, and 15 (Study Days 43, 71, 99, 127, and 155)

Subjects will report to the clinic in the morning of Study Days 43, 71, 99, 127, and 155. Subjects should not take their morning dose(s) of study medication and AED medication prior to reporting to the clinic. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Abbreviated physical examination, including height and weight, and calculation of BMI
- Abbreviated neurological examination
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- 12-lead electrocardiogram (according to the ECHO schedule below)
- Doppler ECHO (this must be obtained after 6 and 12 weeks on study medication; for the 6-week assessment, any time between Study Day 45 and Study Day 69, and for the 12-week assessment, any time between Study Day 87 and Study Day 111)
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry and hematology, and urinalysis; note luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, testosterone, insulin-like growth factor-1 (IGF-1), growth hormone (GH), and coagulation will only be collected on Days 71, 127, and 193)
- Urine THC panel
- Whole blood CBD
- Collect plasma sample for background AED PK evaluation prior to the morning dose of study medication(s) (Visits 7, 9, and 11 [Days 43, 71, 99, respectively] only)
- Tanner Staging for subjects > 7 years of age (Visit 11 [Day 99] only) (Appendix 5)
- Collect and review diary with parent/caregiver
- Dispense diary
- Administer healthcare utilization questions
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- PedsQL Generic Core Scale (Appendix 6)
- BRIEF (Appendix 3)

- QOLCE (Appendix 4)
- PedsQL Family Impact Module (Appendix 6)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- Administer sleep quality and mealtime behavior questions
- Karolinska Sleepiness Scale (Appendix 8)
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.1.6.3 Clinic Visit 17 (Day 183): End of Study/Early Termination

For Cohort 1, the End-of-Study participation for an individual subject occurs after the dose of IMP has been selected for Cohort 2 and the separate, long-term extension trial is open for enrollment.

The End-of-Study visit may also occur if the subject withdraws participation from the study or the Sponsor terminates the study. If the subject withdraws participation from the study, they may on a case-by-case basis, be eligible for entrance into the separate open-label extension trial after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a ZX008 trial. The decision whether to permit open-label extension trial participation resides solely with the Sponsor, who may consult with the site investigator. If the Sponsor terminates the study early, the subject may or may not be offered enrollment into the open-label extension, depending on the reason for termination.

Subjects will visit the clinic for the End-of-Study visit if one the following events occur:

1. The subject withdraws or is withdrawn from participation in the study.
2. The Sponsor terminates the study.
3. The subject completes all study related visits and procedures.

The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Complete physical examination, including height and weight, and calculation of BMI
- Complete neurological examination
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- 12-lead electrocardiogram

- Doppler ECHO (must be performed any time between Day 170 and Visit 17; if subject terminates early from the study, the ECHO should be scheduled as soon as practical. If the Day 57 or Day 99 ECHO was completed ≤30 days prior to early termination, the Visit 17 ECHO will not be performed provided the parent/guardian agrees to bring the subject to the clinic for the cardiac follow-up visit (see Table 10).
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry and hematology, and urinalysis)
- Urine THC panel
- Whole blood CBD
- Collect plasma sample for background AED PK evaluation prior to the morning dose of study medication(s)
- Tanner Staging for subjects > 7 years of age (Appendix 5)
- Collect and review diary with parent/caregiver
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- Healthcare utilization questions
- Dravet syndrome outcomes measures
- Sleep quality and mealtime behavior questions
- Karolinska Sleepiness Scale (Appendix 8)
- PedsQL Generic Core Scale (Appendix 6)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- PedsQL Family Impact Module (Appendix 6)
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

Informed consent for the open-label extension trial must be signed at Visit 17.

6.2 COHORT 2: STUDY PROCEDURES

6.2.1 BASELINE PERIOD (STUDY DAY -42 TO STUDY DAY -1)

The Baseline Period of the study encompasses the screening activities that will occur on Study Day -42 as well as the observation period where subjects will be assessed for baseline seizure activity based on recordings of daily seizure activity entered into a diary.

6.2.2 SCREENING, CLINIC VISIT 1 (STUDY DAY -42 AND STUDY DAY -41)

Screening is the predetermined series of procedures with which each investigator selects an appropriate and representative sample of subjects for enrollment into the study. Select screening data will be documented in the IVR/IWR and eCRF.

Written informed parental or guardian consent and assent of minors (if the subject is capable of providing assent) must be obtained before a subject can start any of the screening procedures. The procedure(s) for obtaining written informed consent and assent of minor (if the subject is capable of providing assent) are described in Section 11.2.

The Screening visit will occur on Study Day -42; however, the procedures may be split over 2 consecutive days (eg, Study Day -43 and Study Day -42, or Study Day -42 and Study Day -41). Splitting the visit procedures across 2 nonsequential days requires the approval of the Medical Monitor. The following procedures will be performed for all subjects before the start of seizure activity observation:

- Obtain written informed consent for the study
- Obtain written informed consent from parent/caregiver to collect EQ-5D-5L ratings of parent/caregiver symptoms and quality of life
- Review inclusion and exclusion criteria
- Record demographic information
- Record medical, neurological, and epilepsy history
- Record current epilepsy status (number/type/duration seizures per month)
- Collect past 6 months (or available duration) of parent/caregiver seizure diary data if available (screen shots of cell phones are acceptable, as are photocopies of paper diaries or print outs) and place in source file
- Administer healthcare utilization questions
- Administer Dravet syndrome outcomes measures
- Record prior medications
- Complete physical examination, including height, weight, and calculation of BMI
- Complete neurological examination
- 12-lead ECG
- Doppler ECHO (this may be obtained any time between Day -42 and Day -21)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, hematology, urinalysis, etc)
- Urine THC panel
- Whole blood CBD
- Obtain blood sample for epilepsy genotype panel (one blood sample drawn between screening and Visit 10)

- Obtain buccal swab for CYP2D6 genotype/phenotype
- C-SSRS Children's Baseline/Screening Assessment (Appendix 2)
- Instruct parent/caregiver on use of diary
- Dispense diary (after above procedures have been concluded)
- Record AEs
- Record AESIs

Only eligible subjects as specified by the inclusion and exclusion criteria with an independently confirmed diagnosis of Dravet syndrome by the Epilepsy Study Consortium will be enrolled into the study.

After enrollment into the study, each subject will be issued a "Subject Card" containing information about the subject's participation in the study. The subject or parent/caregiver will be advised to retain this card on his person for the entire duration of the study so that the investigator or the Sponsor can be contacted in case of emergency.

In certain circumstances the Sponsor may allow subjects who did not meet all inclusion/exclusion criteria at the time of the Screening Visit to have the screening period extended, or to be rescreened for eligibility. In all cases the investigator should consult with the Medical Monitor. Decisions whether to permit rescreening resides solely with the Sponsor.

The decision whether to permit extended screening or rescreening can be influenced by many factors individual to that subject case. Some general principles apply:

1. If baseline seizure screening is extended or the subject is discontinued and then rescreened, the screening period for establishing the baseline seizure frequency will be the immediate 6 weeks before the randomization visit.
2. Subjects who are found to be on a prohibited medication at the screening visit may be weaned off of that medication provided:
    a. Decisions to withdraw a disallowed concomitant medication must be made with the agreement of the prescribing physician.
    b. If the medication has antiepileptic properties, a wash-out of at least 5 half-lives must be completed before collection of baseline seizure data.
    c. If a decision has been made to wean off of a medication without antiepileptic properties and the wash-out period (at least 5 half-lives) is expected to be shorter than 5 weeks, then the subject may remain in screening and chart seizures using the seizure diary.

6.2.3 PHONE VISIT 2 (STUDY DAY -21)

Site personnel will contact the subject via telephone on Study Day -21 and record the following:

- AEs
- AESI
- Concomitant medications

In addition, site personnel will review the diary entries with the parent/caregiver.

6.2.4 CLINIC VISIT 3 (STUDY DAY -1): RANDOMIZATION

This period is intended to ensure that subjects meet the study entry criteria and confirm they have experienced ≥ 6 convulsive seizures during the 6-week Baseline Period, with at least 2 seizures in each 3-week half of the Baseline Period. Subjects must have at least 42 days of prospective diary data at Visit 3. Subjects will report to the clinic in the morning on Study Day -1 to allow for plasma sample collection for AED PK evaluation prior to the morning dose of these medications. Subjects should not take their morning dose(s) of AED medication prior to reporting to the clinic.

The following procedures will be performed on Study Day -1:

- Review inclusion and exclusion criteria
- Review current seizure activity (number/type/duration) from diary since previous visit and calculate the number of convulsive seizures during the first 3 weeks, the second 3 weeks, and over the full 6-weeks of the observation period.
- Record prior medications since previous visit
- Complete physical examination, including height and weight, and calculation of BMI
- Abbreviated neurological examination
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- 12-lead ECG
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, and hematology, and urinalysis)
- Collect plasma sample for background AED PK evaluation prior to the morning dose of study medication(s)
- Urine THC panel
- Whole blood CBD
- Tanner Staging for subjects > 7 years of age (Appendix 5)
- Collect and review diary with parent/caregiver
- Dispense diary
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- Healthcare utilization questions
- PedsQL Generic Core Scale (Appendix 6)
- BRIEF (Appendix 3)

- QOLCE (Appendix 4)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- PedsQL Family Impact Module (Appendix 6)
- Karolinska Sleepiness Scale
- Record AEs
- Record AESI
- When eligibility for the Titration Period is confirmed, randomize (blinded) subject to treatment assignment (ZX008 or placebo)
- Dispense study medication (If administration of the first dose of study medication occurs in the clinic, the next dose should be at least 8 hours later or the following morning. The dose on the following morning will count as Study Day 1.)

6.2.5 TITRATION AND MAINTENANCE PERIODS

6.2.5.1 Titration Period: Day 1

Subjects will take their first dose of study medication in the morning of Study Day 1. Study Day 1 is considered the first day of dosing, even for the subjects that received an in-clinic dose on Study Day -1.

6.2.5.2 Phone or Clinic Visit 4 (Titration Period: Day 8)

Site personnel will contact the subject via telephone or the subject can be reviewed in the clinic on Titration Period Day 8 and record the following:

- AEs
- AESI
- Concomitant medications

In addition, site personnel will review study medication dosing procedure and the diary entries with the parent/caregiver.

6.2.5.3 Clinic Visit 5 (Titration Period: Day 15)

Subjects will report to the clinic in the morning on Titration Period Day 15. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Abbreviated physical examination, including height and weight, and calculation of BMI
- Abbreviated neurological examination
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)

- Collect and review diary with parent/caregiver
- Dispense diary
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- Healthcare resource utilization questions
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.2.5.4 Clinic Visit 6 (Maintenance Period: Day 22)

Subjects will report to the clinic in the morning on Maintenance Period Day 22. Subjects should not take their morning dose(s) of AED medication prior to reporting to the clinic. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Abbreviated physical examination, including height and weight, and calculation of BMI
- Abbreviated neurological examination
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry and hematology, and urinalysis)
- Urine THC panel
- Whole blood CBD
- Collect plasma sample for background AED PK evaluation prior to the morning dose of study medication(s)
- Collect and review diary with parent/caregiver
- Administer sleep quality and mealtime behavior questions
- Administer Karolinska Sleepiness Scale (Appendix 8)
- Dispense diary
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.2.5.5 Phone Visit 7 (Maintenance Period: Day 36)

Site personnel will contact the subject via telephone on Maintenance Period Day 36 and record the following:

- AEs
- AESI
- Concomitant medications
- Healthcare utilization questions

In addition, site personnel will review study medication dosing procedure and the diary entries with the parent/caregiver.

6.2.5.6 Clinic Visit 8 (Maintenance Period: Day 50)

Subjects will report to the clinic in the morning on Maintenance Period Day 50. Subjects should not take their morning dose(s) of study medication and AED medication prior to reporting to the clinic. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Abbreviated physical examination, including height and weight, and calculation of BMI **(Note: if the subject's weight is ±25% of the weight at Day -1, the IMP dose will be recalculated)**
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- 12-lead ECG
- Doppler ECHO (this must be obtained any time between Day 40 and Day 54)
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry and hematology, and urinalysis)
- Urine THC panel
- Whole blood CBD
- Collect plasma sample for background AED PK evaluation prior to the morning dose of study medication(s)
- Collect and review diary with parent/caregiver
- Dispense diary
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- PedsQL Generic Core Scale (Appendix 6)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL Family Impact Module (Appendix 6)
- CGI-I (assessed by parent/caregiver)

- CGI-I (assessed by investigator)
- Administer sleep quality and mealtime behavior questions
- Karolinska Sleepiness Scale (Appendix 8)
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.2.5.7 Phone Visit 9 (Maintenance Period: Day 64)

Site personnel will contact the subject via telephone on Maintenance Period Day 64 and record the following:

- AEs
- AESI
- Concomitant medications
- Healthcare utilization questions

In addition, site personnel will review study medication dosing procedure and the diary entries with the parent/caregiver.

6.2.5.8 Clinic Visit 10 (Maintenance Period Day: 78)

Subjects will report to the clinic on Maintenance Period Day 78. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Abbreviated physical examination, including height and weight, and calculation of BMI
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry and hematology, and urinalysis)
- Urine THC panel
- Whole blood CBD
- Collect and review diary with parent/caregiver
- Dispense diary
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- Administer sleep quality and mealtime behavior questions

- Karolinska Sleepiness Scale (Appendix 8)
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

At Clinic Visit 10, compliant subjects who have tolerated IMP should be presented with the ICF for the open-label extension trial. Informed consent for the open-label extension trial must be signed at Visit 12 or earlier in order to enter the open-label extension trial.

6.2.5.9 Phone Visit 11 (Maintenance Period: Day 92)

Site personnel will contact the subject via telephone on Maintenance Period Day 92 and record the following:

- AEs
- AESI
- Concomitant Medications
- Healthcare utilization questions

In addition, site personnel will review study medication dosing procedure and the diary\entries with the parent/caregiver.

6.2.5.10 Clinic Visit 12 (End of Study/Early Termination: Day 106)

The End-of-Study participation for an individual subject occurs after he/she has received IMP for 12 weeks in the Maintenance Period. At the End-of-Study visit, the subject may enroll into the separate extension trial if they have completed 12 weeks of treatment in the Maintenance Period. Other circumstances for participation in the extension trial are described in Section 4.8.

The End-of-Study visit may also occur if the subject withdraws participation from the study or the Sponsor terminates the study. If the subject withdraws participation from the study, they may on a case-by-case basis, be eligible for entrance into the separate open-label extension trial after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a ZX008 trial. The decision whether to permit open-label extension trial participation resides solely with the Sponsor, who may consult with the site investigator. If the Sponsor terminates the study early, the subject may or may not be offered enrollment into the open-label extension, depending on the reason for termination.

Subjects will visit the clinic for the End-of-Study visit if one the following events occur:

- The subject withdraws or is withdrawn from participation in the study.
- The Sponsor terminates the study.
- The subject completes all study related visits and procedures.

The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Complete physical examination, including height and weight, and calculation of BMI
- Complete neurological examination
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- 12-lead ECG
- Doppler ECHO (must be performed any time between Day 90 and Visit 13; if subject terminates early from the study, the ECHO should be scheduled as soon as practical. If the Day 43 ECHO was completed ≤30 days prior to early termination, the Visit 12 ECHO will not be performed provided the parent/guardian agrees to bring the subject to the clinic for the cardiac follow-up visit (see Table 10).
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry and hematology, and urinalysis)
- Urine THC panel
- Whole blood CBD
- Collect plasma sample for background AED PK evaluation prior to the morning dose of study medication(s)
- Tanner Staging for subjects > 7 years of age (Appendix 5)
- Collect and review diary with parent/caregiver
- Dispense diary
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- Healthcare utilization questions
- Sleep quality and mealtime behavior questions
- Karolinska Sleepiness Scale (Appendix 8)
- PedsQL Generic Core Scale (Appendix 6)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- PedsQL Family Impact Module (Appendix 6)
- Record AEs
- Record AESI

- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication for taper for subjects not enrolling in the open-label extension trial
- Dispense study medication for transition for subjects enrolling in the open-label extension trial

Informed consent for the open-label extension trial must be signed at Visit 12 (if not signed earlier) in order to enter the open-label extension trial.

6.2.5.11 Follow-up Visit (Clinic Visit 13; Day 120)

Subjects will report to the clinic in the morning of Visit 13. Subjects should not take their last dose of study medication or morning dose of antiepileptic medication prior to reporting to the clinic so that 4 blood samples can be obtained for steady-state PK.

For subjects entering the open-label extension trial, the subject will visit the clinic on Visit 13 (Day 120). The following will be recorded/performed and the subject will immediately be enrolled in that separate study:

- Review current seizure activity (number/type/duration) from diary since previous visit
- AEs
- AESI
- Concomitant medications
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Collect plasma sample for ZX008 PK evaluation prior to the morning dose of study (last dose of Protocol 1504 study medication) and their usual AED medication(s)
- Collect additional plasma samples for ZX008 PK evaluation at 1, 2, and 4-6 hours post-dose

If the subject does not enter the open-label extension trial (or discontinues from the study early), the subject will visit the clinic on Visit 13 (Day 120) (or 14 days after the day of discontinuation). The following will be recorded/performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- AEs
- AESI
- Concomitant medications
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

6.2.6 CARDIAC FOLLOW-UP VISIT (COHORT 1: CLINIC VISITS 18, 19/COHORT 2: CLINIC VISIT 14; 3-6 MONTHS AFTER LAST DOSE OF STUDY MEDICATION)

If the subject completes the study but does not enter the open-label extension trial or discontinues from the study early, the subject will return to the clinic for follow-up cardiac testing (ECHO, ECG, and in some cases physical examination). The timing and frequency of exams are presented in Table 10. Subjects on blinded medication who are found to have been on placebo are not required to participate in follow-up testing once the blind is broken at the end of the study. As the ECHO and ECG will be administered in a separate clinic from the pediatric neurology clinic, an asymptomatic subject receiving a second follow-up ECHO and ECG does not require a physical examination.

Subjects with positive findings on ECHO, ECG and/or physical examination should continue to be followed until the finding is resolved or stable and unlikely to change, with reports submitted as AESI to the ZX008 safety database.

Table 10. Schedule of Post-Treatment Cardiac Follow-up

	Duration of Blinded[a] or Fenfluramine Treatment				
Parameter	Less than 2 weeks Cumulative	2 to 4 weeks	> 4 and < 13 weeks	> 13 weeks	Have had any cardiac sign or symptom regardless of the time on study drug[b]
ECHO	No	Yes, 3 months post-treatment	Yes, 3 months post-treatment	Yes, 3-6 months post-treatment	Yes, 3 and 6 months post-treatment, and until resolved, or stable and unlikely to change
ECG	No	Yes, 3 months post-treatment	Yes, 3 months post-treatment	Yes, 3-6 months post-treatment	Yes, 3 and 6 months post-treatment and until resolved, or stable and unlikely to change
Physical examination	No	Yes, 3 months post-treatment	Yes, 3 months post-treatment	Yes, 3 months post treatment only	Yes, 3 and 6 months post-treatment, and until resolved, or stable and unlikely to change

ECG = electrocardiogram; ECHO = echocardiogram; IPCAB = International Pediatric Cardiology Advisory Board
[a] If blind is broken at the end of the study and a subject revealed to have taken only placebo, no further testing is required.
[b] Positive sign or symptom includes any development of valve thickening or regurgitation "trace" or greater in mitral, aortic; mild or greater in pulmonary, tricuspid), or sign or symptom indicative of potential pulmonary hypertension as adjudicated by the IPCAB.

6.3 ESTIMATED BLOOD VOLUME COLLECTION

The maximum total blood volume collected during the first 15 days of the study for Cohort 1 will be approximately 63.4 mL for the PK portion of the study, as outlined in Table 11. The maximum total blood volume collected during the transition period of the study for Cohort 1 will be approximately 122.1 mL over 24 weeks.

Table 11. Estimated Blood Volume Collection for Cohort 1

Assessment	Screening (Day -14 to -1)	Day 1-2	Day 15	Total Screening-Day 15	Transition Period Days 43, 71, 99, 127, 155, 183
Clinical chemistry & prolactin	2 x 5 mL	--	--	10 mL	6 x 10 mL
LH, FSH, estradiol, testosterone	1 x 4 mL			4 mL	3 x 4 mL (every 8 weeks)
Hematology	2 x 2mL			4 mL	6 x 2mL
Epilepsy Genotyping	5 mL			5 mL	--
IGF-1, GH	1 x 2 mL			2 mL	3 x 2 mL (every 8 weeks)
Coagulation	2 x 2.7mL			5.4 mL	3 x 2.7 mL (every 8 weeks)
Cannabidiol	2 x 2 mL			4 mL	6 x 2 mL
PK sample (ZX008 and background AED)	--	6 x 4mL		24 mL	
AED plasma sample	--		2mL	2 mL	6 x 2 mL
Volume for flushing indwelling catheter	--	6 x 0.5mL		3 mL	
Approximate total blood volume per subject	34.4 mL	27mL	2 mL	63.4mL	**122.1 mL**

AED=antiepileptic drug; FSH=follicle stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; LH-luteinizing hormone; PK=pharmacokinetic

The maximum total blood volume collected during the study for Cohort 2 (clinical laboratory testing, genotyping, and PK) will be approximately 117.2 mL, as outlined in Table 12.

Table 12. Estimated Blood Volume Collection for Cohort 2

Assessment	Baseline Period		Titration + Maintenance Period					
	Screening (Day -42 to -41)	Randomization Day -1	Day 22	Day 50	Day 78	Day 106	Visit 13 Day 120	Total
Clinical chemistry, prolactin	5 mL	5 mL	5 mL	5 mL	5 mL	5 mL		42 mL
LH, FSH, estradiol, testosterone	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	--	
Hematology	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	--	12 mL
Epilepsy Genotyping	5 mL	--	--	--	--	--	--	5 mL
IGF-1 and GH	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	--	12 mL
Coagulation	2.7 mL	2.7 mL	2.7 mL	2.7 mL	2.7 mL	2.7 mL	--	16,2 mL
Cannabidiol	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	--	12 mL
ZX008 PK sample	--	--			--	--	4 × 2 mL	8 mL
AED plasma sample		1 x 2 mL	1 x 2 mL	1 x 2 mL	--	1 x 2 mL		8 mL
Volume for flushing indwelling catheter	--	--	--	--	--	--	4 x 0.5 mL	2 mL
Approximate total blood volume per subject	20.7 mL	17.7 mL	17.7 mL	17.7 mL	15.7 mL	17.7 mL	10 mL	**117.2 mL**

AED=antiepileptic drug; FSH=follicle stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; LH-luteinizing hormone; PK=pharmacokinetics

In concordance with The Seattle Children's Research Foundation Guidance (Appendix 9), blood collection volumes for children weighing up to 15 kg will be:

- the maximum allowable volume of blood in one draw is 22-30 mL (2.5% of total blood volume)
- the maximum in a 30-day period is 44-60 mL

On Day 120/Visit 13 the PK blood draw will be completed as the priority and the blood draw for chemistry and hematology will be skipped for those subjects who weigh less than 13.5 kg, unless medical concerns (for example, from previous tests or reported side effects) prioritize chemistry and/or hematology.

If blood collection is restricted due to volume or due to inability to draw adequate volume, collection should be prioritized as shown in Table 13.

Table 13: Priorities for Blood Sample Collections

Assessment	Priority
ZX008 PK sample	Priority 1
Clinical chemistry	Priority 2
Cannabidiol	Priority 2
AED plasma sample	Priority 2
LH, FSH, estradiol, testosterone, GH, prolactin	Priority 3
Hematology	Priority 3
IGF-1	Priority 4
Genotyping	One time collection any time during or after screening
Coagulation	One time collection any time before PK day

AED = antiepileptic drug; FSH=follicle stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; LH = luteinizing hormone; PK=pharmacokinetics

7. EFFICACY, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

For an overview of the study variables and measurement times, see Schedule of Assessments (Table 1 for Cohort 1 and Table 2 for Cohort 2).

Variables used to measure treatment compliance with respect to administration of the IMP are described in Section 5.8.

7.1 EFFICACY ASSESSMENTS: COHORT 2

Baseline is defined as the seizure frequency during the 6-week Baseline Period.

Retrospective diary data (up to 6 months) will be collected, if available, for an exploratory evaluation of the duration of baseline data capture on interpretation of post-treatment effect.

For all questionnaires and rating scales, the same evaluator (at the clinical site and parent/caregiver) will complete the assessments for the duration of the study. Substitutions at the clinic with another rater that has established inter-rater reliability is acceptable on an infrequent basis. For the in-clinic questionnaires and rating scales completed by the parent/caregiver, if the same parent/caregiver cannot complete the questionnaire/rating scale at a visit, the questionnaire/rating scale will not be completed. For the diary, the same parent/caregiver will complete all entries throughout the study.

7.1.1 Seizure Assessments

Seizure frequency by type and duration (< 2 minutes, 2-10 minutes, > 10 minutes) will be

recorded daily by the parent/caregiver in a diary. Seizure types include:

A: Hemiclonic (note lateralization – right body, left body, or independent right and left)
B1: Focal With or Without Clear, Observable Motor Signs
B2: Focal Without Clear, Observable Motor Signs
C: Secondarily Generalized Tonic Clonic (evolving to bilateral convulsive seizure from focal seizure)
D: Generalized Tonic Clonic Convulsion
E: Absence or Atypical Absence
F: Myoclonic
G: Tonic
H: Atonic
I: Clonic
J: Tonic/Atonic (cannot differentiate; also known as 'drop attack')
K: Infantile Spasms (if under 3 years of age)
L: Epileptic Spasms (if 3 years of age and older)

O: Other

Efficacy endpoints that will be derived from the diary data include frequency of convulsive seizures and of all seizures, and the number/duration of seizure free intervals.

Seizures that evolve into SE will be captured by type and duration (> 10 minutes) as are all seizures. The diagnosis of SE made by a medical professional should be entered as an AE or SAE if a prolonged seizure or series of seizures persists for 30 minutes or longer, regardless of administration of rescue medication. SE lasting for less than 30 minutes should be entered as an AE, unless one of the other SAE criteria (eg, hospitalization) are met. If this incident involves multiple seizures close in time, the SE definition applies if the seizures are close together such that consciousness is not regained between ictal events.

7.1.2 Clinical Global Impression - Improvement (Exploratory Endpoint)

Both the parent/caregiver and the investigator will rate their global impression of the subject's condition throughout the study according to the schedule in Table 1 and Table 2.

The Clinical Global Impression (CGI) scale measures the change in the subject's clinical status from a specific point in time, ie, the Baseline Period. The CGI rating scale permits a global evaluation of the subject's improvement over time. The severity of a patient's condition is rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) as follows:

1=very much improved

2=much improved
3=minimally improved
4= no change
5=minimally worse
6=much worse
7=very much worse

The parent/caregiver will be asked to indicate the appropriate response that adequately describes how their child's symptoms have improved or worsened relative to baseline before the beginning of the study (before any study drug was taken).

The investigator will be asked to indicate the appropriate response that adequately describes how the subject's symptoms have improved or worsened relative to baseline before the beginning of the study (before any study drug was taken). A paragraph describing symptoms and function at baseline will be documented in the source file prior to rating.

7.1.3 Sleep Quality and Mealtime Behavior Questions (Exploratory Endpoint)

The parent/caregiver will be asked to indicate the appropriate response that adequately describes their child's sleep quality and eating behavior since starting IMP based on the following questions:

1. Since your child has started taking the study medication in this study, have you noticed that s/he has been waking in the middle of the night or very early in the morning more than usual?

- My child's sleep is more disturbed than it was before s/he started the study medication
- My child's sleep patterns are the same as they were before starting the study medication
- My child sleeps better than s/he did before starting the study medication

2. Since your child has started taking the study medication in this study, have you noticed that s/he has had a change in their mealtime behavior?

- My child has worse mealtime behavior since starting the study medication
- My child's mealtime behavior has not changed since starting the study medication
- My child has improved his/her mealtime behavior since starting the study medication

7.1.4 Karolinska Sleepiness Scale (Exploratory Endpoint)

The Karolinska Sleepiness Scale (Appendix 8) will be administered according to the schedule in Table 1 and Table 2. The Karolinska Sleepiness scale is a self-report scale that measures the subject's drowsiness. It is a 9-point verbally anchored scale, which ranges from 'extremely

alert' at one end of the scale to 'extremely sleepy – fighting sleep' at the other end of the scale. Within this study, the scale will be completed by the observer in an exploratory manner.

7.1.5 Quality of Life in Childhood Epilepsy Scale

The QOLCE (Appendix 4), 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, will be conducted according to the schedule in Table 1 and Table 2. The QOLCE has been validated in children aged 4 and older, and there are published data on the use of the QOLCE in children with epilepsy as young as 2 years of age (Sabaz 2000; Talarska 2007).

7.1.6 PedsQL Scale

The PedsQL (Appendix 6) is a modular approach to measuring HRQOL in healthy children and adolescents and those with acute and chronic health conditions. The PedsQL Measurement Model includes both generic core scales and disease-specific modules in one measurement system. The 23-item PedsQL Generic Core Scales, which will be used in this study, were designed to measure the core dimensions of health as delineated by the World Health Organization, as well as role (school) functioning. The 4 Multidimensional Scales and 3 Summary Scores are:

Scales	Summary Scores
Physical Functioning (8 items)	**Total Scale Score** (23 items)
Emotional Functioning (5 items)	**Physical Health Summary Score** (8 items)
Social Functioning(5 items)	**Psychosocial Health Summary Score** (15 items)
School Functioning (5 items)	

This scale is completed by the parent/caregiver on behalf of the subject. It will be used according to the schedule in Table 1 and Table 2.

7.1.7 Parent/Caregiver Quality of Life

The impact on the quality of life of the parent/caregiver responsible for a patient with Dravet syndrome will be assessed according to the schedule in Table 1 and Table 2 using 2 scales: the EQ-5D-5L and the PedsQL Family Impact Module. Parents/caregivers who do not give consent to collect these ratings scales will not complete them. The same parent/caregiver should complete these ratings throughout the study. If that person is not available at the visit, the scales should not be completed.

The EQ-5D-5L (Appendix 7) is a standardized measure of health status used to provide a simple, generic assessment for clinical and economic appraisal. It consists of 6 questions and can be completed in less than 10 minutes.

The PedsQL Family Impact module (Appendix 6) is designed to measure the impact of pediatric chronic health conditions on parents and the family by measuring parent self-reported physical, emotional, social, and cognitive functioning, communication, worry, and family daily activities relationships. The parent/caregiver will be asked to indicate the appropriate response that adequately describes how the care of their child with Dravet syndrome has impacted their quality of life using the scales described above. The PedsQL Family Impact module will not be assessed in the Netherlands.

7.1.8 Healthcare Utilization Questions (Exploratory Endpoint)

In order to better understand the healthcare resource burden associated with the management of Dravet syndrome, caregivers will be asked which of the following hospital and community-based healthcare services they had interactions with over the preceding month: emergency room services, ambulance, planned and unplanned hospitalization, family physician services, speech and language therapy, occupational therapy, and physical therapy. This information will be captured in the CRF as outlined in Table 1 and Table 2.

7.1.9 Dravet Syndrome Outcome Measures (Exploratory Endpoint)

The European Medicines Agency recommends that the assessment of efficacy in clinical investigations of medicinal products in the treatment of epileptic disorders should be based primarily upon seizure frequency/occurrence (EMA 2010). Whilst of upmost importance, it is also recognized that the impact of Dravet syndrome as experienced by patients and carers extends beyond the direct impact of seizures (Nolan 2008; Desnous 2011).

Dravet syndrome is associated with clinical manifestations other than tonic-clonic seizures, many of which have a strong impact on individual and family well-being, and persist into adulthood: multiple seizure types, deficits in cognition and executive function, sleep disturbances, and behavioral disturbances. A Dravet syndrome composite endpoint will be created using a series of outcome measures from the protocol to create a composite endpoint to assess treatment of Dravet syndrome without emphasis on a single endpoint. The outcomes under evaluation in this study will include measures for example such as seizure frequency, behaviour, quality of sleep, and others. The measures to select the composite are identified as part of a project with physician interviews and interviews with patient's families and are part of a project on multi-dimensional outcome measures.

7.2 SAFETY ASSESSMENTS

7.2.1 Demographics, Medical/Neurological/Epilepsy History, and Pre-Study Medication

Subject demographics (sex, age, height, weight, and BMI), all ongoing conditions and relevant medical history from the past 5 years (including all major hospitalizations and surgeries) as well as the subject's current medical status will be recorded at the Screening visit. Significant medications taken during the 30 days prior to the Screening visit will be documented. Medication history will be updated as outlined in Table 1 and Table 2.

7.2.2 Physical Examinations

Complete and abbreviated physical examinations, including height and weight, will be conducted by the investigator or designee during the study as outlined in Table 1 and Table 2. A complete standard of care physical examination for each subject will be performed and will cover the following body systems: general appearance, skin, eyes, ears, nose, throat, heart, lungs, abdomen, neurological system, lymph nodes, spine, and extremities. An abbreviated physical examination for each subject will cover the following body systems: heart, lungs, and follow up of other systems as appropriate based on last exam and reported AEs.

Any unfavorable findings not present at screening considered by the investigator as clinically significant, occurring at any point in the study will be documented in the eCRF as an AE.

7.2.3 Neurological Examinations

Complete and abbreviated neurological examination will be conducted by the investigator or designee during the study as outlined in Table 1 and Table 2. A complete standard of care neurological examination for each subject will be performed and will cover the following: cranial nerves, muscle strength and tone, reflexes, coordination, sensory function, and gait. An abbreviated neurological follow-up examination for each subject will evaluate any symptoms or systems found to be abnormal and unstable or potentially unstable that might evolve during study treatment, or to investigate any reported or observed AEs.

Any unfavorable findings not present at screening considered by the investigator as clinically significant, occurring at any point in the study will be documented in the eCRF as an AE.

7.2.4 Vital Signs

Vital signs including blood pressure, heart rate, temperature, and respiratory rate will be documented for subjects during study as outlined in Table 1 and Table 2. Subjects will be sitting for 5 minutes prior to the vital signs being obtained. Blood pressure should be assessed on the same arm for each time of determination.

7.2.5 Laboratory Measurements

Laboratory safety parameters will be analyzed using standard validated methods.

The following parameters will be assessed by the laboratory as described in Table 1 and Table 2:

- Hematology: hemoglobin, hematocrit, erythrocytes, erythrocyte mean corpuscular volume, leukocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets

- Blood Biochemistry: albumin (ALB), alkaline phosphatase (AP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bicarbonate, blood urea nitrogen (BUN), calcium (Ca), 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), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid.

- Tests of growth and precocious puberty: Growth hormone (GH), insulin-like growth factor-1 (IGF-1, low sensitivity), prolactin, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), testosterone, estradiol

- Epilepsy genotype panel

- Buccal swab for CYP2D6 genotyping

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

- Whole blood cannabidiol (CBD)

- Urinalysis: analysis for pH, glucose, ketones, nitrite, protein, bilirubin, urobilinogen, leukocyte esterase, and occult blood. Microscopic analysis will be performed for blood, all cell types, and casts.

- Urine pregnancy test: Urine pregnancy testing will be performed in female subjects of childbearing potential.

- Urine THC panel

The investigator will receive the laboratory report from the central laboratory. After reviewing the report and evaluating any results that are outside the normal range, the investigator must sign and date the laboratory report.

Tests resulting in abnormal laboratory values that have been classified by the investigator as abnormal, clinically significant should be repeated as soon as possible after receiving the laboratory report to rule out laboratory errors.

At Screening any laboratory values that deviate from the reference ranges and are considered by the investigator as clinically relevant must be documented on the medical history form of the eCRF. Any deviation outside of the reference range considered by the investigator as clinically significant (ie, classified as an abnormal, clinically significant value) at any visit after screening will be documented in the eCRF as an AE (see Section 8).

7.2.6 Plasma Sample for Concomitant Antiepileptic Drug(s)

Plasma samples to ensure that concomitant antiepileptic drug(s) (AEDs) dosing is within an acceptable range will be conducted during the study as outlined in Table 1 and Table 2. Samples collected at Visit 6 will be analyzed after collection as a safety measure. Samples collected at other time points will be analyzed at study end and do not constitute safety assessments.

7.3 ADVERSE EVENTS

Adverse events will be collected from the time of signing the informed consent form/assent form until the end of the study, including the follow-up clinic visit. Details of the definitions and categorization of AEs, and procedures for the reporting of AEs, are available in Section 8.

Severity and causality of AEs will be evaluated according to the criteria specified in Section 8.2 and Section 8.3, respectively. The observation period for AE reporting is specified in Section 8.4. At the beginning of each visit at the study site, the study personnel will specifically inquire about any AEs that might have occurred since the last study site visit. All AEs will be recorded on the appropriate eCRF page.

7.3.1 Electrocardiograms

Twelve-lead ECGs will be conducted during study as outlined in Table 1 and Table 2 after the subject has been in the supine position resting for ≥5 minutes. Heart rate, PR duration, QRS duration, QT duration, QTcF (Fridericia's correction formula), and will be read centrally.

7.3.2 Doppler Echocardiography

Doppler echocardiography will be conducted at a facility with experience for the subject's age during study as outlined in Table 1 and Table 2. 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's IPCAB prior to study initiation. These thresholds are provided in Table 16. A manual of proper ECHO technique for sites is provided in a separate document.

7.3.3 Tanner Staging

Tanner Staging (Appendix 5) will be assessed for subjects > 7 years old during the study as outlined in Table 1 and Table 2. Conceptually, pubertal maturation can be described in terms of sequence, timing, and tempo. Puberty consists of a series of predictable events, and the sequence of changes in secondary sexual characteristics has been categorized by several groups. The staging system used most frequently was published by Marshall and Tanner (1969, 1970) and the sequence of changes are commonly referred to as 'Tanner stages'.

7.3.4 Columbia-Suicide Severity Rating Scale

C-SSRS (Appendix 2) will be assessed during study as outlined in Table 1 and Table 2. The C-SSRS is a validated rating scale that assesses suicidal behavior and ideation. The scale is used to assess and track suicide events and provides a summary measure of suicidal tendency. The C-SSRS version 6/23/10 (Children's Baseline/Screening and Children's Since Last Visit) will be used in this study as appropriate for the age and level of intellectual development.

Subjects who are younger than 7 years chronologically, or who are judged by the investigator not to have the mental capacity to understand the questions as specified on the C-SSRS, will not complete the rating. The investigator should use his/her judgment to substitute intellectually-appropriate questions to probe the tendency for self-harm.

If a subject with the intellectual capacity to complete the C-SSRS has their 7th birthday during the study, use of the C-SSRS should be initiated at subsequent visits.

7.3.5 Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF is a standardized, validated rating scale to measure executive function in children ages 2-18 years within the home and school environments; it will be assessed according to the schedule in Table 1 and Table 2. The BRIEF measures multiple aspects of executive

functioning; scales include Inhibit (control impulses; stop behavior), Shift (move freely from one activity/situation to another; transition; problem-solving flexibility), Emotional Control (modulate emotional responses appropriately), Initiate (begin activity; generate ideas), Working Memory (hold information in mind for purpose of completing task), Plan/Organize/Organization of Materials (anticipate future events; set goals; develop steps; grasp main ideas), and Monitor (check work; assess own performance). The BRIEF will be used to assess cognitive function in subjects who are ≥ 5 years of age at baseline. The pre-school version of the BRIEF (BRIEF-P) will be used to assess cognitive function in children < 5 years of age at baseline.

7.4 PHARMACOKINETIC ASSESSMENTS

Cohort 1: Blood samples for PK assessments of fenfluramine and its metabolite (norfenfluramine), CLB and its metabolite N-CLB, STP, and VPA will be obtained from all subjects via an indwelling catheter. Prior to obtaining the PK sample, about 0.5 mL should be drawn off and discarded. Samples will be collected within one hour prior to dosing (pre-dose), and at 2, 4, 8, 12, and 24-36 hours post-dose. Six samples (one pre-dose and five post-dose) will be collected from each subject for a total of approximately 27 mL.

Cohort 2: Blood samples for PK assessment (2 mL) of fenfluramine and its metabolite (norfenfluramine) will be obtained at the following time points:

- Visit 13: within 1 hour prior to the morning dose, and 1, 2, and 4-6 hours after the morning dose.

A total of 4 PK samples will be drawn for each subject for a total of approximately 8 mL of blood.

When blood draws for PK coincide with other assessments, the PK draws take precedence.

The procedure for the collection and handling of PK samples is outlined in a separate study manual.

7.5 APPROPRIATENESS OF MEASUREMENTS

All of the variables assessed are standard tests or procedures that are commonly used in studies of this type.

8. ADVERSE EVENTS

8.1 DEFINITIONS

8.1.1 Adverse Events

According to ICH guidelines, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. The period of observation for adverse events extends from the time the subject gives informed consent until the end of study.

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study. Exacerbation of seizures is considered an AE if there was an increase in frequency beyond the subject's typical pre-study fluctuations, or in the event that seizures lengthen in duration in a clinically meaningful way compared with baseline, or if a new seizure type emerges.
- A clinical event occurring after consent but before IMP administration.
- Intercurrent illnesses with an onset after administration of IMP.

Adverse events do not include:

- Medical or surgical procedures (the condition that leads to the procedure is the AE, eg, tonsillitis is the AE if a tonsillectomy is performed)
- Situations where an untoward medical occurrence has not taken place. For example:
    - Planned hospitalizations due to pre-existing conditions, which have not worsened.
    - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).

- Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy).

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the investigator as clinically significant must be recorded in the eCRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

1. Laboratory parameters are already beyond the reference range, unless a further increase/decrease can be considered an exacerbation of a pre-existing condition.

2. Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, hemolysis) and flagged as such by the laboratory in the laboratory report.

3. Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life).

4. An abnormal laboratory value that cannot be confirmed after a repeated analysis, preferably in the same laboratory (eg, the previous result could be marked as not valid and should not necessarily be reported as an AE).

8.1.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

1. **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.

2. **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.

3. **Requires in-patient hospitalization or prolongation of existing hospitalization** – The Sponsor considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.

4. **Results in persistent or significant disability or incapacity.**

5. **Is a congenital anomaly or birth defect.**

6. **Is medically significant** – A medically significant event is defined as an event that does not meet any of the other 5 SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion. Anaphylaxis that is successfully treated by administration of epinephrine prior to other sequelae is an example of a potentially medically important event.

For the purpose of data collection in this study, a prolonged seizure or series of seizures from which the subject does not regain consciousness between ictal events, that is at least 30 minutes in duration, is termed SE. A single episode of SE in a 24-hour period, regardless of whether rescue medication was administered, should be entered in the AE log as well as in the seizure diary. If two or more episodes occur within 24 hours, each lasting 30 minutes or more, an SAE of SE should be recorded. Hospitalization to manage SE, regardless of the number of episodes, should be reported as an SAE.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

8.1.3 Adverse Events of Special Interest

As per ICH guidance (E2F Development Safety Update Report 2011), the Sponsor has identified the following AESI for the ZX008 program (Table 14).

Table 14. Adverse Events of Special Interest

Metabolic/Endocrine
1. Elevated prolactin level ≥2x above the upper limit of normal (ULN)
2. Hypoglycemia – serum blood glucose more than 20% below the glucose level on Day -1 value or more than 10% below LLN (reference range 60 – 140 mg/dL)
Neuropsychiatric
13. Suicidal thoughts, ideation or gestures
LLN = lower limit of normal; ULN = upper limit of normal

8.1.4 Adverse Events Requiring Hospitalization

If a subject is treated in a medical facility (hospital, emergency room, free-standing clinic) related to the occurrence of any AE, the following data will be collected to model health care utilization in patients with Dravet syndrome: AE/reason for hospitalization/clinic visit; duration of the visit in hours/days; admission to intensive care unit; and name/number of procedures performed, including but not limited to, electroencephalogram, ECG, ECHO, positive emission tomography (PET) scan, MRI, x-ray, computed tomography (CT) scan, surgery, and lumbar puncture/spinal tap.

8.2 SEVERITY OF ADVERSE EVENTS

The severity of AEs (whether nonserious or serious AEs) is to be assessed by the investigator as follows (Table 15).

Table 15. Severity Definition of Adverse Events

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Clinical Data Interchange Standards Consortium Study Data Tabulation Model Severity Intensity Scale for Adverse Event Terminology

8.3 CAUSALITY OF ADVERSE EVENTS

The causal relationship of an AE to IMP must always be assessed by the investigator. All AEs will be classified as either **related** or **not related** to IMP. If a causality assessment is not provided for an AE (including an SAE), then that AE will be considered as related to IMP.

The degree of certainty with which an AE is attributed to IMP or an alternative cause (eg, natural history of the underlying disease, concomitant medications) will be determined by how well the event can be understood in terms of:

- Known pharmacology of ZX008
- Clinically and/or pathophysiologically plausible context
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor)
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with IMP drug withdrawal or reproduced on rechallenge)

The following classifications should be used in categorization of relatedness:

1. Not Related: Concomitant illness, accident or event with no reasonable association with study drug.

2. Related: The event follows a reasonable temporal sequence from administration of study drug and is definitive pharmacologically; cannot to be attributed to concurrent disease or other factors or medications. A clinically reasonable response should be observed if the study drug is withdrawn or dose reduced.

8.4 OBSERVATION PERIOD FOR ADVERSE EVENT REPORTING

The observation period for AE and SAE reporting in an individual subject will start at the time of giving written informed consent for participation in the current study and finish 15 days after the last dose of study drug or the last visit, whichever is later. For subjects who enroll in the open-label extension trial, ongoing AEs will be followed in that study.

If the investigator becomes aware of an SAE that has started after the observation period has finished, and the event could in some way be associated with IMP (irrespective of whether or not it is considered by the investigator to be causally related to IMP), then this must also be reported to the Sponsor (see Section 8.6).

8.5 ADVERSE EVENT REPORTING

8.5.1 Adverse Events

At each clinical evaluation, the investigator (or delegate) will determine whether any AEs have occurred. Adverse events will be recorded in the AE page of the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms. The investigator must follow up on the course of an AE until resolution or stabilization. If an AE is ongoing after the end of study visit, the AE will continue to be followed up until resolution or stabilization.

If, during the study period, a subject presents with a pre-existing condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History section of the eCRF.

8.6 SERIOUS ADVERSE EVENTS REPORTING

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting 1994).

In the event of an SAE the investigator or delegate must:

1. Enter all relevant information in the AE page of the eCRF.
2. Inform the Medical Monitor or the Sponsor of the SAE via email or telephone within

24 hours of becoming aware of the SAE.

3. Follow the initial notification with a completed SAE report form. The SAE form must be emailed or faxed to Inventive Health Care within 24 hours of becoming aware of the SAE.

All SAEs that occur during the course of the study, beginning the day Informed Consent is signed, whether or not causally related to IMP must be reported immediately via telephone or email (within 24 hours of the investigator becoming aware of the event) to the Sponsor or the Medical Monitor.

Contact details and guidance for reporting SAEs will be provided to study site before the study starts.

8.6.1 Requirements for Immediate Reporting of Serious Adverse Events

The minimum reporting requirements for immediate reporting of SAEs include:

1. Identifiable subject
2. Suspected drug product
3. Event description
4. Identifiable reporting source

In addition, the investigator must:

1. Report all SAEs to the relevant IRB/IEC within the timeframe specified by the IRB/IEC.
2. Submit follow-up reports to the Sponsor Global Clinical Safety and Pharmacovigilance and the Medical Monitor until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
3. Ensure that the AE term(s) and causality assessment for all SAEs is entered in the eCRF.

If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event before notifying the Sponsor.

When submitting SAE reports to the Sponsor, subjects should be identified only by their subject number and study number. The investigator should not include the subject's name and address.

SAE Update reports can be submitted to the Sponsor any time that additional relevant information becomes available. In cases of death, the investigator should supply the Sponsor and the IEC/IRB (as applicable, see Section 8.7) with any additional requested information as it becomes available (eg, autopsy reports and detailed medical reports). Once an SAE is reported to the Sponsor's Safety Group, a Safety Specialist may contact the investigator with follow-up questions.

The procedure to be followed if an ongoing AE becomes an SAE after the end of the observation period for AEs is described in Section 8.9.

8.7 REPORTING OF SERIOUS ADVERSE EVENTS BY INVESTIGATOR TO IEC/IRB

The timeframe within an IEC/IRB must be notified of a death or an unexpected SAE considered at least possibly related to the IMP is stipulated by each individual IEC/IRB. The investigator is responsible for complying with the requirements for IEC/IRB notification. The investigator will notify the relevant IEC/IRB within the applicable timeframe by forwarding the safety report (eg, MedWatch/CIOMS form) completed by the Sponsor for the notifiable event.

8.8 REPORTING OF EVENTS OTHER THAN SERIOUS ADVERSE EVENTS BY INVESTIGATOR TO SPONSOR

Even if none of the criteria for an SAE are fulfilled, any of the following events must be reported by the investigator to the Medical Monitor within 72 hours from the time the investigator is notified.

1. Hypersensitivity reactions
2. Pulmonary hypertension
3. Cardiac symptoms requiring intervention, or valvulopathy, if identified outside of study-related monitoring

8.9 FOLLOW-UP OF ADVERSE EVENTS

Every effort should be made to follow-up subjects who continue to experience an AE or an SAE on completion of the study or until the AE resolves. All follow-up information (and attempted follow-up contacts) should be documented in the subject's medical records. Details of the subject's progress should also be submitted to the Sponsor's Global Clinical Safety and Pharmacovigilance and the Medical Monitor.

Subjects who are discontinued from the study or complete the study and have been found to have any signs of valvulopathy or pulmonary hypertension on ECHO will be followed until the condition has resolved or stabilized where no further changes are likely, for a minimum of

6 months from the last dose of study medication, unless it is determined after unblinding that the subject did not receive ZX008. In the event of an SAE a blood sample for ZX008 and AED PK should be collected as soon as feasible (this is not required for SAEs that occur before dosing with study medication).

8.9.1 Follow-up of Echocardiogram Findings

All ECHOs will be evaluated by a central reader from BioMedical Systems, Inc. (BMS), in consultation with the IPCAB, if warranted. 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 16 describes the severity of ECHO findings with the level of increasing oversight if the subject is to remain in the study.

Table 16. 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 (eg, VPA, CLB, 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 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 appropriate.
    a. If both of these conditions are not met, the subject is discontinued from treatment.
3. The investigator prepares a case history and rationale for continuation to be submitted to the IDSMC for review, including consideration of effects on seizures and comorbidities.
4. The Co-Chairs of the IPCAB are alerted to the request and prepare, after consultation with BMS, an evaluation of the cardiopulmonary risks and proposed monitoring plan if applicable, for submission to the IDSMC.
5. IDSMC will review the submissions from the Investigator and the IPCAB and unblind the subject treatment if warranted.
6. IDSMC makes 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 by the IDSMC. MINIMAL efficacy criteria for IDSMC 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 (eg, VPA, CLB, 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. The investigator prepares a case history and rationale for continuation to be submitted to the IDSMC for review, which includes effects of study medication on seizures and comorbidities related to Dravet syndrome.
4. The Co-Chairs of the IPCAB are alerted to the request, and in consultation with BMS prepare an evaluation of the risks and proposed monitoring plan if applicable for submission to the IDSMC.
5. IDSMC will review the submission from the Investigator and the IPCAB and unblind the subject treatment if warranted.
6. IDSMC makes 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

8.10 PREGNANCY

This study is open to female and male subjects. Whenever possible, a pregnancy in a female subject or the female partner of a male subject exposed to IMP should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after

delivery, should be reported by the investigator to the Sponsor using a pregnancy reporting/outcome form.

9. DATA HANDLING PROCEDURES

9.1 RECORDING OF DATA

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, study-required information and data, and other notes as appropriate. These records constitute source data.

An eCRF and a subject diary will be provided by the Sponsor (or delegate) for each subject enrolled into the study. Study site staff will enter data directly into the validated electronic data capture (EDC) system by completing the eCRF via a secure internet connection. The investigator is responsible for ensuring accurate and proper completion of the eCRF and subject diary for recording data according to the instructions given in the eCRF and subject diary.

All entries in the eCRF must be backed up by the relevant source data at the study site. All source data will be kept according to all applicable regulatory requirements (see Section 12.8). Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

Data entry in the eCRF and subject diary must be completed in a timely manner so that they always reflect the latest observations on the subjects enrolled in the study.

The subject's diary will be completed by the parent/caregiver at home. Data entries will be reviewed by the investigator for completion and consistency.

9.2 DATA QUALITY ASSURANCE

An initiation meeting will be held before starting the study, during which the study design, procedures to be followed, and measures for ensuring standardized performance will be explained by a delegate from the Sponsor, and a common understanding of the requirements of the study will be reached with the investigator and other relevant personnel at the study site.

Data generated throughout the study will be monitored and the data entered in the eCRFs will be checked against the subject records for completeness and accuracy. The Sponsor's study monitor will perform this function.

The computer system used for study data handling will be fully 21 Code of Federal Regulations (CFR) Part 11 compliant. All creation, modification or deletion of electronic study records will be documented through an automated Audit Trail. Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically for consistency and

plausibility. Data queries will be generated for questionable data and response clarification will be sought from the investigator. These data queries must be resolved in a timely manner by the investigator (or delegate).

9.3 RECORD RETENTION

A study document binder will be provided by the Sponsor for the investigator at each site for all requisite study documents (constituting the "Investigator Study File").

Following completion of the study, the investigator will retain copies of the approved study protocol, ICF, relevant source documents, and all other supporting documentation related to the study according to applicable regulatory requirements.

The investigator is responsible for archiving the Investigator Study File, the subject's records, and the source data according to applicable regulatory requirements. These documents have to be archived for at least 15 years or at least 2 years after the last approval of a marketing application in an ICH region, but should be retained for longer if required by regulatory requirements or by agreement with the Sponsor.

If the investigator can no longer maintain the archive of study records (eg, due to retirement or relocation), the Sponsor must be informed in writing about any change in responsibility for record retention, including the name of the new responsible party, contact information, and location of the study records. Records may not be destroyed without prior written consent from the Sponsor.

10. STATISTICS

10.1 DETERMINATION OF SAMPLE SIZE

No formal hypothesis tests are planned for the PK endpoints studied in Cohort 1. Thus, the sample size for Cohort 1 is based on practical considerations including the expected availability of appropriate subjects. The PK data from Cohort 1 will be used in combination with PBPK models that are being developed using robust data from adults and from existing PBPK models for the concomitant medications. In this way, the data from ZX008-1504 will be leveraged with existing PK information on fenfluramine, stiripentol, clobazam and valproate acid to confirm the expectations derived from the mechanism-based PBPK models. Analysis of the data in this way allows for the confirmation of the appropriateness of the extension of the PBPK model from adults to children and a robust assessment of the potential for a drug-drug interaction between ZX008 and stiripentol while limiting exposure to a smaller number of patients. The 18-20 subjects targeted for the PK phase of the study is expected to be sufficient to allow for the extension of the PK information gained in the ongoing PK study in adults and existing PBPK models to pediatric patients with Dravet syndrome.

The sample size for Cohort 2 is based on results from Study 1, the randomized, placebo-controlled study in subjects with Dravet syndrome sponsored by Zogenix (Lagae 2017). The standard deviation (SD) of the percentage change in seizure frequency from baseline to the end of study (Day 99) was 50% for the 0.8 mg/kg/day group and 69% for the 0.2 mg/kg/day. For the sample size calculation for Cohort 2, the SD is assumed to be intermediate between the SDs observed in the high and low dose groups in Study 1. Assuming an SD of 58, and using a two-sided test at the α=0.05 significance level, a sample size of 45 subjects per treatment group affords 90% power to detect a difference in mean change in seizure frequency from baseline of 40 percentage points. Thus, the total sample size for Cohort 2 is planned to be approximately 90 subjects (45 per arm).

10.2 ANALYSIS POPULATIONS (COHORT 2)

10.2.1 Safety (SAF) Population

All safety analyses will be performed on the Safety (SAF) Population defined as all randomized subjects who receive at least one dose of ZX008 or placebo. Subjects will be analyzed according to the treatment actually received.

10.2.2 Modified Intent-to-Treat (mITT) Population

The modified Intent-to-Treat (mITT) Population is defined as all randomized subjects who receive at least one dose of ZX008 or placebo and for whom at least one week of diary data are available. Subjects will be analyzed according to the treatment group to which they were randomized. The primary comparison of ZX008 0.5 mg/kg/day to placebo, as well as key secondary analyses, will be performed on the mITT Population.

10.2.3 Per Protocol (PP) Population

The Per Protocol (PP) Population is defined as all randomized subjects who receive at least one dose of ZX008 or placebo, complete the entire 12 week Maintenance Period, and have no major protocol deviations that would have a significant impact on clinical outcome. Subjects will be analyzed according to the treatment they received. The primary and key secondary efficacy analyses will be repeated on the PP Population if there are substantial differences in the makeup of the mITT and PP Populations.

10.3 TREATMENT GROUPS

Subjects in Cohort 2 will be randomly assigned to treatment with either ZX008 (0.5 mg/kg/day, maximum dose 20 mg/day) or placebo.

10.4 TREATMENT PERIODS

10.4.1 Cohort 1 Treatment Periods

PK Evaluation Period

The PK Evaluation begins when a subject receives his or her single dose of ZX008 and continues for 15 days afterward.

Transition Period

For participating subjects, the transition period begins immediately after the PK Evaluation period and continues for a maximum of 24 weeks.

10.4.2 Cohort 2 Treatment Periods

Baseline Period

The Baseline Period covers the approximately 42-day span just prior to randomization and the start of treatment. The baseline frequency of convulsive seizures will be calculated from data collected during this period.

Titration Period

The Titration Period covers the time period during which subjects are titrated to the assigned randomized dose. It begins on the first day of treatment (Study Day 1) and concludes on Study Day 21. The Titration Period applies to all subjects including placebo recipients.

Maintenance Period

The Maintenance Period covers the 12 weeks following the end of the titration period.

Titration + Maintenance (T + M) Period

The T + M period combines the Titration and Maintenance periods. The T + M period is considered the treatment period.

Follow-up Period

The Follow-up Period begins immediately at the end of T + M period and extends through Visit 13 (Day 120).

10.5 STATISTICAL ANALYSES AND METHODS

All efficacy, safety, and PK data will be summarized. Continuous data will be summarized using descriptive statistics including means, SDs, medians, lower and upper quartiles, and ranges. Categorical variables will be summarized with frequencies and percentages. Confidence intervals will be calculated for key parameters or estimates as warranted.

A complete description of the statistical analyses and methods will be available in a statistical analysis plan (SAP), which will be finalized before the database is locked.

10.5.1 Efficacy Analyses

The primary and key secondary efficacy analyses that compare ZX008 to placebo will be performed using subjects from Cohort 2 only. Efficacy endpoints, such as convulsive seizure frequency, assessed in Cohort 1 during the Transition Period will be summarized with descriptive statistics only.

10.5.1.1 Primary Efficacy Analysis – Cohort 2

The primary efficacy endpoint is the change in the mean convulsive seizure frequency (MCSF) per 28 days between the Baseline and T + M periods. The MCSF will be calculated from all available data collected during the Baseline or T + M Periods.

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with treatment group (ZX008 or placebo) and age group (< 6 years, ≥ 6 years) as factors, and with baseline frequency as a covariate. The primary analysis will compare the ZX008 group to the placebo group using a two-sided test at the α=0.05 level of significance.

Since the ANCOVA used in the primary analysis relies on assumptions of normality, the primary endpoint will also be analyzed using a nonparametric method that does not require as stringent assumptions. A nonparametric test will be used to compare the ZX008 group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the nonparametric test will be used to assess the primary objective.

Additional analyses will compare the percentage changes between the baseline MCSF and the MCSF measured independently during the Titration Period alone and the Maintenance Period alone.

10.5.1.2 Key Secondary Analyses – Cohort 2

The first key secondary endpoint – the proportion of subjects who achieve a $\geq$ 50% reduction from baseline in convulsive seizure frequency – is derived directly from the primary endpoint. That is, the proportion of subjects in the ZX008 group who have a change in convulsive

frequency of at least 50 percentage points will be compared to the analogous proportion in the placebo group. The comparison will be made using a logistic regression model that incorporates the same factors and covariates as the ANCOVA used in the primary analysis. The analyses will be performed using data collected over the T + M period.

The longest interval between convulsive seizures will be calculated for each subject over the entire T + M period. The ZX008 and placebo groups will be compared using a Wilcoxon test.

Whenever feasible, secondary analyses will be repeated using post-treatment data collected during the Titration Period alone and during the Maintenance Period alone.

10.5.1.3 Multiplicity Strategy and Testing Hierarchy – Cohort 2

The efficacy analyses will employ a serial gatekeeper strategy to maintain the Type 1 error rate at α=0.05 across the family of analyses that support the primary and key secondary objectives. The strategy specifies a hierarchy of significance tests where each test acts as a gatekeeper to the tests below it.

The primary and key secondary endpoints will be assessed in the following order entailing comparisons between the ZX008 and placebo groups on

- The change in MCSF from baseline.
- The proportion of subjects who achieve a $\geq$ 50% reduction from baseline in convulsive seizure frequency.
- The longest convulsive seizure-free interval.

10.5.2 Safety Analyses

Summaries of safety data for subjects in Cohort 2 will be presented by treatment – ZX008 at assigned dose or placebo – separately for the Titration, Maintenance and T + M periods. The number and percentage of subjects in each treatment group with AEs will be displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs by severity and relationship to study drug will also be presented. A separate summary will be provided for all SAEs. Selected summaries will be repeated broken out by age group, ie, for ages < 6 years and $\geq$ 6 years.

Hematology and chemistry laboratory results for subjects in Cohort 2 will be summarized by descriptive statistics at each time point available. Mean change from baseline will also be calculated for continuous hematology and chemistry results at all time points available.

Laboratory tests, vital signs, physical examinations, neurological examinations, ECG, Doppler ECHO, C-SSRS, Tanner Staging results, etc, will be summarized appropriately, by treatment. All safety summaries for subjects in Cohort 2 will be based on the SAF Population.

For subjects in Cohort 1, safety will be summarized by treatment regimen and by treatment period, either the PK Evaluation or Transition Period. Summaries will also be produced for all subjects in Cohort 1 combined regardless of regimen. AEs, laboratory results, vital signs and other endpoints will be described using similar statistics as those used for Cohort 2.

10.5.3 Pharmacokinetic Analyses

All data from Cohort 1 will be evaluated using PK analysis methods and the methods will be described in detail in a separate PK analysis plan. While the approaches will be similar for all analytes of interest (fenfluramine/norfenfluramine, CLB/n-desmethylclobazam, VPA, and STP), they will be tailored to the availability of previous PK information and/or existing PK models. The full methods and results of the population PK analysis of data from this study will be provided in a separate report.

The clinical study report will contain a brief summary of the analysis including: overviews of the models applied to the concentration-time data for each analyte, the population mean and interindividual variability estimates (as appropriate) from the fits of the population PK models; summary statistics of the plasma concentrations by PK sampling time by regimen.

Each of the three regimens from Cohort 1 will be compared to the others based on the PK measurements obtained for each analyte. For example, a linear model incorporating log-transformed data will be used to estimate the geometric mean ratio and the 90% confidence interval (CI) of fenfluramine AUC from time zero to time=t (AUC_{0-t}) measured from the ZX008 0.2 mg/kg/day + CLB + VPA + STP group (Regimen 3) to the analogous quantity measured from the ZX008 0.2 mg/kg/day + CLB + VPA group (Regimen 1). Analogous techniques will be applied to comparisons based on the other analytes: norfenfluramine, STP, CLB, N-CLB, and VPA. The set of analyses will be repeated for each pair of regimens.

The plasma concentration data from Cohort 2 will also be analyzed using population PK methods. Fenfluramine/norfenfluramine concentration-time data from subjects enrolled in Cohort 2 will be pooled with that from subjects in Cohort 1 in order to assess the applicability of the population PK model to predict plasma concentrations from multiple dosing. Modifications to the model will be made as necessary to achieve an adequate fit to the steady-state PK data. Plasma PK exposure (AUC_{0-t}) will be derived for each patient from Cohort 2 who undergoes PK sampling. The results of the analysis of PK data collected in subjects from Cohort 2 will be reported separately.

10.5.4 Analysis of Exploratory Endpoints

As stated above, one of the aims of this research program is to determine a core set of patient relevant outcomes to understand the impact of Dravet syndrome beyond seizure frequency. To meet this objective a set of core outcome measures have been identified to include in this trial. The selection of instruments was driven by data from in depth interviews with formal and informal carers of young people with Dravet syndrome. Some of these measures have not been used previously in Dravet syndrome. Therefore, in addition to testing the main study hypotheses an additional SAP will be developed to describe the exploratory analyses that test the psychometric performance (or measurement accuracy) of the core outcome measures. The performance of the scales will be benchmarked against seizure burden as an objective endpoint. This is based on a working hypothesis that Dravet syndrome patients' subjective outcomes (such as HRQL) are heavily influenced by their seizure burden (including nature of seizures and frequency). Therefore, changes in seizure burden should predict changes in the core outcome measures. This hypothesis will be tested using psychometric methods.

10.6 ANALYSES PROVIDED TO AN INDEPENDENT DATA AND SAFETY MONITORING COMMITTEE

A safety oversight monitoring plan will be in place with an IDSMC evaluating data from the subjects. Details will be provided in the IDSMC charter. The IDSMC's primary responsibility is to ensure that study subjects are not exposed to unanticipated harm that could have been prevented by timely review and intervention. The IDSMC is established to review safety data at predefined time points, and to recommend to the Sponsor whether to continue, modify, or terminate the study as necessary. The IDSMC is composed of expert permanent members who cover relevant specialties (neurology, cardiology, pediatrics, and statistics). The IDSMC members may request assistance from a number of additional and hoc members if needed.

11. ETHICAL & REGULATORY CONSIDERATIONS

11.1 ETHICAL CONSIDERATIONS

The procedures set out in this study protocol are designed to ensure that the Sponsor and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 Guideline. ICH GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, and that the clinical study data are credible.

The study will also be carried out according to all applicable international and national regulatory requirements.

The Sponsor and the investigator must inform each other (eg, during a study initiation visit, via e-mail, etc) that all ethical and legal requirements have been met before the first subject is enrolled into the study.

11.2 INFORMED CONSENT

The investigator is responsible for obtaining a subject's written informed consent to participate in the study.

A Subject Information Sheet and a master ICF will be prepared by the Sponsor according to the provisions of ICH GCP and local legal requirements.

All subjects will be informed that the study will be registered in the public database at ClinicalTrials.gov in accordance with the FDA Amendments Act of 2007 (Section 12.3).

Before undergoing screening procedures for possible enrollment into the study, subjects must be informed, in an understandable form, about the nature, scope, and possible consequences of the study. This information must be given orally to subjects by a physician or medically qualified person (according to applicable regulatory requirements) who is well informed about the nature, scope, and possible consequences of the study. Written information about the study will also be provided in a Subject Information Sheet. The date on which this oral and written information on the study was provided to the subject, and by whom it was provided, must be documented in the ICF.

As specified in ICH GCP Section 4.8 and the US 21CFR Section 50.25, the informed consent discussion must emphasize that participation in the study is voluntary and that subjects have the right to withdraw their consent at any time without giving a reason and without any disadvantage for their subsequent care.

Subjects must be given ample time and opportunity to inquire about details of the study and to consider their participation in the study. If, after reading the Subject Information Sheet and the ICF, consent is given to participate in the study, then the ICF must be signed and personally dated by the subject and the person conducting the informed consent discussion (and an impartial witness, if required). The subject will be provided with a copy of the signed ICF.

Verification of the signed ICF will be recorded in the subject's eCRF. The original signed ICF will be filed with the subject's records and a copy will be placed in the Investigator Study File.

The Subject Information Sheet and ICF have to be approved by the IEC/IRB before they can be used in the study.

The Subject Information Sheet and ICF must be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revision of these

documents must be approved by the IEC/IRB before they can be used in the study. Subjects must be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation in the study. The communication of this information should be documented by having all parties concerned sign and personally date the revised ICF.

Subject or Subject's Legally Acceptable Representative Unable to Read

If a subject is unable to read, or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information provided to the subject, parent or guardian has been read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should also sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Assent for Subjects Under the Age of Consent (Pediatric Subjects)

All subjects are under the age of consent (ie, pediatric subjects under 18 years of age); the written informed consent of a legally acceptable representative is required. Pediatric subjects who can understand the nature, scope, and possible consequences of the study must also give their assent, orally and/or in writing via the assent document, as appropriate. After the ICF and any other written information to be provided to subjects has been read and explained to the subject and the subject's legally acceptable representative, and after the subject and the legally acceptable representative have orally consented to the subject's participation in the study and, if capable of doing so, the subject has signed and personally dated the assent document, the legally acceptable representative should sign and personally date the ICF. By signing the ICF, the legally acceptable representative attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject, and that assent was freely given by the subject.

11.3 REGULATORY CONSIDERATIONS AND INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

The Sponsor (or delegate) will submit the appropriate documents to all applicable competent regulatory authorities and IEC/IRBs, and will await all relevant approval before enrolling any subjects into the study. Written approval should mention the study protocol by study title, study number, and version date.

The Sponsor (delegate) will ensure that the investigators conduct the study as stipulated in this study protocol and in accordance with all applicable regulatory requirements. The Sponsor (delegate) is obliged to obtain evidence of the investigator's qualification to perform the clinical study. Therefore, the investigator has to provide a signed and dated copy of his or her professional curriculum vitae (prepared no more than 2 years beforehand and preferably written in English) before the start of the study, including information on his or her experience in conducting clinical studies according to ICH GCP and other applicable regulatory requirements.

Written notification of the identity and occupation of the members of the IEC/IRB is also required by the Sponsor (delegate). Should the IEC/IRB be unwilling to provide this information, a letter stating that the committee was constituted in accordance with applicable regulatory requirements should be provided.

11.4 PROTOCOL COMPLIANCE

The investigator must conduct the study in compliance with this study protocol as agreed to by the Sponsor and, if required, by any competent regulatory authority, and which has been approved by, or given a favorable opinion by, the IEC/IRB.

The investigator should not implement any deviation from, or changes to, the study protocol without agreement by the Sponsor (delegate) and prior review and documented approval or favorable opinion from the IEC/IRB of an amendment to the study protocol. Exceptions include only cases of medical emergency to address immediate hazards to study subjects, or when the changes involve only logistic or administrative aspects of the study.

In the event of a medical emergency, the investigator at each site may institute any medical procedures deemed appropriate to address an immediate hazard to a subject without prior IEC/IRB approval or favorable opinion. As soon as possible, the implemented deviation or change, the reason(s) for it, and, if appropriate, the proposed study protocol amendment(s) should be submitted to:

- The Sponsor (delegate) for agreement.
- The IEC/IRB for review and approval or favorable opinion (if required).
- The applicable competent regulatory authority (if required).

Details of the procedure for implementing study protocol amendments are available in Section 12.10.

At the earliest opportunity, the investigator (or delegate) must inform the Sponsor (delegate) about any notable protocol deviations and explain any deviation from the approved study protocol in the eCRF and/or in the Protocol Deviation Log, if applicable.

12. ADMINISTRATIVE ASPECTS

12.1 CLINICAL TRIAL AGREEMENT

This study will be conducted under a Clinical Trial Agreement between the Sponsor (or delegate) and the respective institutions representing the study sites. Any financial support given to the study sites will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement, which must be signed before the start of any study related procedures, will clearly delineate the responsibilities and obligations of the investigator and the Sponsor (delegate), and will form the contractual basis upon which the study will be conducted.

12.2 FINANCIAL DISCLOSURE BY INVESTIGATOR

Prior to study initiation, the investigator and any subinvestigator(s) to be directly involved in the treatment or evaluation of study subjects at each study site will disclose to the Sponsor (delegate) any relevant financial or proprietary interests in either the study product or the Sponsor company. The appropriate disclosure form(s) will be provided by the Sponsor (delegate) for this purpose. Any relevant updates to the financial disclosure information that occur during the conduct of the study, or during one year after completion of the study, will be provided by the investigator and subinvestigator(s) to the Sponsor (delegate). All financial disclosure information provided by the investigator and subinvestigator(s) will be submitted to appropriate competent authorities according to the applicable regulatory requirements.

12.3 CLINICAL STUDY REGISTRATION AND RESULTS DISCLOSURE

The Sponsor will provide the relevant study protocol information in a public database (ClinicalTrials.gov) before or at commencement of the study, as required by the 2007 FDA Amendments Act. The Sponsor (delegate) may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential subject contacts the Sponsor regarding participation in the study, the investigator agrees that the Sponsor (delegate) may forward the relevant study site and contact details to the subject. Based on the inclusion and exclusion criteria for the study, the investigator will assess the suitability of the subject for enrollment into the study. Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record on ClinicalTrials.gov.

12.4 STUDY FILES AND MATERIALS

Before the start of any study related procedures, all essential documents specified by ICH GCP and other applicable regulations must be available in the relevant files maintained by the Sponsor (or delegate) and the investigator. An Investigator Study File prepared by the Sponsor (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. A list of personnel and organizations responsible for conduct of the study as well as the list of investigators will be included in the Investigator Study File. The respective files will be kept and updated by the Sponsor (or delegate) and the investigator, as applicable.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by the Sponsor's study monitor (or delegate) to determine that all required documentation is present and correct (see Section 12.9).

The study may be audited or inspected by qualified delegates from the Sponsor or a competent regulatory authority (see Section 12.11).

12.5 INITIATION OF THE STUDY

Before the start of the study at each study site, the Sponsor's study monitor (or delegate) will visit the study site to ensure adequacy of the facilities and to discuss responsibilities regarding study protocol adherence with the investigator and other personnel involved in the study.

The investigator may not enroll any subjects into the study before the Sponsor has received written approval or a favorable opinion from the IEC/IRB for conducting the study and a formal meeting has been conducted by the Sponsor's study monitor (or delegate) to initiate the study (study initiation visit). This meeting will include an inventory of study supplies and a detailed review of the study protocol and procedures, the eCRF, IMP accountability, and the subject diary.

12.6 SUBJECT REIMBURSEMENT

Where relevant, subjects will be reimbursed for reasonable travel costs associated with participation in this study, after presentation of receipts for the travel in question, at a rate to be approved by the IEC/IRB. Subjects will not be paid for participating in the study.

12.7 LIABILITY AND INSURANCE

The civil liability of the involved parties with respect to financial loss due to personal injury and other damage that may arise as a result of this study being conducted are governed by the applicable legal requirement(s).

The Sponsor will provide insurance to the investigator if required by the applicable regulatory and legal requirement(s).

If required by local law, subjects taking part in this study will be insured against any injury caused by the study in accordance with the applicable regulatory and legal requirement(s).

12.8 SUBJECT IDENTIFICATION AND CONFIDENTIALITY

All study documents, including the study protocol and eCRFs, are the confidential property of the Sponsor and should be treated as such.

All subjects screened for the study will be documented in a screening log in compliance with the requirements of individual study sites. Subjects not enrolled into the study will be documented as such in the screening log together with the reason for not having been enrolled.

The investigator will maintain a personal list of subject names and subject numbers (Subject Identification List) for participants in the study to enable records to be identified at a later date. These records should be retained in a confidential manner for the duration stipulated by applicable regulatory requirements. All subject names will be kept in confidence and will not be revealed to the Sponsor. Subject names must be made unreadable on any documents made available to the Sponsor.

Subjects participating in the study will be identified in the eCRF by the subject number allotted to them during the study.

The ICF will include a statement that all study findings, irrespective of the medium on which they are stored, will be handled in strictest confidence in accordance with applicable data protection laws (eg, the European Data Protection Directive [95/46/EC] and the USA Health Insurance Portability and Accountability Act, and will be evaluated by the Sponsor and/or a competent regulatory authority in an anonymized form. The subjects are also to be informed that their medical records may be audited or inspected by qualified delegates from the Sponsor or a competent regulatory authority. The subject's written consent authorizing direct access to his medical records, and computer processing and publishing of his anonymous personal data, must be obtained prior to participation in the study.

A subject's identity will be disclosed by the investigator only in case of emergency (ie, to address any immediate health hazard).

12.9 MONITORING OF THE STUDY

The investigator at each site will allow the Sponsor's study monitor (or delegate) reasonable access to the eCRFs and direct access to related source documents for monitoring purposes as frequently as the Sponsor deems necessary. These documents include records of tests

performed as a requirement for participating in the study as well as other medical records required to confirm information contained in the eCRF, such as past history and secondary diagnoses.

Before each monitoring visit, the investigator (or delegate) should record all data generated since the last monitoring visit in the eCRF. The investigator and other relevant personnel at each study site will be expected to cooperate with the Sponsor's study monitor to assist in providing any missing information.

The study monitor will require access to the Investigator Study File to ensure completeness of all documentation required for the study. The study monitor will ensure that the investigator at each site has been provided with adequate means for organization and filing of study documentation (see Section 12.4).

The date on which the study monitor (or delegate) visits the study site will be recorded in the Site Visit Log. During monitoring visits, the study site's coordinator (if applicable) and the investigator should be available, the source documentation should be accessible, and a suitable environment should be provided for the study monitor to review study related documentation.

The main objectives of monitoring visits conducted by the study monitor include:

- Resolution of any problems.
- Examination of all study documentation for completion, adherence to the study protocol, and possible AEs.
- Clarification of inconsistencies or missing data.
- Verification of study data against source documents.
- Checks that investigator obligations have been fulfilled.
- Review of ICFs and dates of consent.
- Inspection of IMP with respect to storage, labeling, and documentation.
- Drug accountability

After each subject's visit to the study site, the investigator (or delegate) will ensure that all data have been entered into the eCRF correctly and in a timely manner, after which the investigator will sign the eCRF.

12.10 PROTOCOL AMENDMENTS

A "substantial" amendment of a study protocol is any written description of change(s) to, or formal clarification of, a study protocol that may have a significant impact on the safety or physical or mental integrity of subjects, the scientific value of the study, the conduct or management of the study, or the quality or safety of any IMP used in the study. The IEC/IRB must approve all substantial protocol amendments prior to their implementation. If required by applicable local regulatory requirements, the local regulatory authority must also approve all substantial protocol amendments prior to their implementation.

A "non-substantial" amendment of a study protocol includes minor corrections or clarifications that have no significant impact on the way the study is to be conducted and has no effect on the safety of participating subjects (eg, change in study monitor, contact details, etc). If required by applicable local regulatory requirements, the IEC/IRB, and/or the local regulatory authority should be notified of all non-substantial protocol amendments. The substantial and non-substantial protocol amendments will be integrated into an updated study protocol at the discretion of the Sponsor if the changes to the original study protocol are numerous, or if required by applicable regulatory requirements.

12.11 AUDITS AND INSPECTIONS

The study may be audited or inspected by qualified delegates from the Sponsor or a competent regulatory authority.

In the event of an audit by the Sponsor, the investigator must make all study related documentation available to the auditor(s). Regulatory authorities may request access to all study related documentation, including source documents, for inspection and copying in keeping with applicable regulations. The Sponsor will immediately notify the investigator (or vice versa) of an upcoming audit or inspection.

If an audit or inspection occurs, the investigator and relevant personnel at the study site must allocate sufficient time to discuss the findings and any relevant issues.

12.12 CLINICAL STUDY REPORT

After completion of the study, a clinical study report covering clinical and statistical aspects of the study will be prepared by the Sponsor (or delegate) in consultation with the coordinating investigator. As required by the applicable regulatory requirements, the clinical study report will be signed by the Sponsor's responsible medical officer as well as the coordinating investigator (if applicable).

Progress reports and/or a summary of the clinical study report will be provided to the IEC/IRB and competent regulatory authorities in accordance with applicable requirements.

12.13 USE OF DATA AND PUBLICATIONS

The rights and obligations of investigators and the Sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study (see Section 12.1).

For multicenter studies, the first publication must be based upon all data obtained from all analyses, as stipulated in the study protocol by the biostatistician and not by the investigators. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of study sites before the full, initial publication is available or 5 years after the last clinical study visit, whichever is later, unless this has been agreed to by all other investigators and by the Sponsor.

The Sponsor must receive a copy of any intended communications in advance of the proposed submission date. This is to allow the Sponsor time to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential and/or proprietary information is not inadvertently divulged, to provide any relevant supplementary information, and to allow establishment of co-authorship (as appropriate). The authorship of communications arising from pooled data will include investigators from study sites that contributed data as well as relevant personnel from the Sponsor. Ownership of all data will remain with the Sponsor.

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ZX008 Investigator's Brochure Version 3, January 5, 2016.

14. APPENDICES

APPENDIX 1 – LIST OF PROHIBITED CONCOMITANT MEDICATIONS AND FOODS

Generic Name	Generic Name
alfentanil	naratriptan
almotriptan	nefazodone
alprenolol	nortriptyline
amitriptyline	ondansetron
amphetamine	oxcarbazepine
astemizole	oxycodone
atomoxetine	paroxetine
bufuralol	perphenazine
bupropion	phenacetin
buspirone	phenobarbital
cafergot	phenytoin
cannabidiol	promethazine
carbamazepine	propafenone
cerivastatin	retigabine/ezogabine
citalopram	risperidone
clomipramine	ritonavir
codeine	rizatriptan
cyproheptadine	selegiline
desipramine	sertraline
dextromethorphan	Stiripentol (Cohort 1, Regimens 1 and 2)
duloxetine	sumatriptan
eletriptan	telaprevir
encainide	THC and derivatives
ergotamine tartrate	tramadol
eslicarbazepine	trazodone
felbamate	vortioxetine

fentanyl	zolmitriptan
fluoxetine	zuclopenthixol
fluvoxamine	
frovatriptan	
imipramine	
levacetylmethadol (LAAM)	
linezolid	
meperidine	
methadone	
metoclopramide	
mexiletine	

APPENDIX 2 – COLUMBIA – SUICIDE SEVERTY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline/Screening

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION				
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime		Past 6 Months	
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
INTENSITY OF IDEATION				
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe		Most Severe	
Frequency ***How many times have you had these thoughts?*** ***Write response*** _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____		____	

 C-SSRS—Children's Baseline/Screening (Version 6/23/10) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

 C-SSRS—Children's Baseline/Screening (Version 6/23/10) Page 2 of 2

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response*** _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

 C-SSRS—Children's Since Last Visit (Version 6/23/10) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with on coming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 3 – BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION

BRIEF®-P

Behavior Rating Inventory of Executive Function®– Preschool Version

RATING FORM

Gerard A. Gioia, PhD, Kimberly Andrews Espy, PhD, and Peter K. Isquith, PhD

Instructions to Parents and Teachers

On the following pages is a list of statements that describe young children. We would like to know if the child has had *problems* with these behaviors *during the past 6 months*. Please answer *all the items* the best that you can. Please do not skip any items. Think about the child as you read these statements and circle:

N	if the behavior is	**Never** a problem
S	if the behavior is	**Sometimes** a problem
O	if the behavior is	**Often** a problem

For example, if having tantrums when told "No" is **never** a problem, you would circle **N** for this item:

Has tantrums when told "No" (N) S O

If you make a mistake or want to change your answer, ***DO NOT ERASE***. Instead draw an **X** through the answer you want to change and then circle the correct answer:

Has tantrums when told "No" (X) (S) O

Before you begin answering the items, please fill in the child's name, gender, age, and birth date, as well as your name, relationship to the child, and today's date in the spaces provided at the top of the next page. If you are the child's teacher or child care provider, please check the box next to the response that best describes how well you know the child and indicate how long you have known the child in the space provided.

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Child's Name _____ Gender _____ Age _____ Birth Date ___/___/___

Your Name _____ Today's Date ___/___/___

Relationship to Child: ☐ Mother ☐ Father ☐ Teacher* ☐ Other* _____

How well do you know the child? ☐ Not Well ☐ Moderately Well ☐ Very Well *Have known the child for ____ ☐ months ☐ years.

During the past 6 months, how often has each of the following behaviors been a *problem*?	Never	Sometimes	Often
1. Overreacts to small problems	N	S	O
2. When given two things to do, remembers only the first or last	N	S	O
3. Is unaware of how his/her behavior affects or bothers others	N	S	O
4. When instructed to clean up, puts things away in a disorganized, random way	N	S	O
5. Becomes upset with new situations	N	S	O
6. Has explosive, angry outbursts	N	S	O
7. Has trouble carrying out the actions needed to complete tasks (such as trying one puzzle piece at a time, cleaning up to earn a reward)	N	S	O
8. Does not stop laughing at funny things or events when others stop	N	S	O
9. Needs to be told to begin a task even when willing to do it	N	S	O
10. Has trouble adjusting to new people (such as babysitter, teacher, friend, or day care worker)	N	S	O
11. Becomes upset too easily	N	S	O
12. Has trouble concentrating on games, puzzles, or play activities	N	S	O
13. Has to be more closely supervised than similar playmates	N	S	O
14. When sent to get something, forgets what he/she is supposed to get	N	S	O
15. Is upset by a change in plans or routine (for example, order of daily activities, adding last minute errands to schedule, change in driving route to store)	N	S	O
16. Has outbursts for little reason	N	S	O
17. Repeats the same mistakes over and over even after help is given	N	S	O
18. Acts wilder or sillier than others in groups (such as birthday parties, play group)	N	S	O
19. Cannot find clothes, shoes, toys, or books even when he/she has been given specific instructions	N	S	O
20. Takes a long time to feel comfortable in new places or situations (such as visiting distant relatives or new friends)	N	S	O
21. Mood changes frequently	N	S	O
22. Makes silly mistakes on things he/she can do	N	S	O
23. Is fidgety, restless, or squirmy	N	S	O
24. Has trouble following established routines for sleeping, eating, or play activities	N	S	O
25. Is bothered by loud noises, bright lights, or certain smells	N	S	O
26. Small events trigger big reactions	N	S	O
27. Has trouble with activities or tasks that have more than one step	N	S	O
28. Is impulsive	N	S	O
29. Has trouble thinking of a different way to solve a problem or complete an activity when stuck	N	S	O
30. Is disturbed by changes in the environment (such as new furniture, things in room moved around, or new clothes)	N	S	O

During the past 6 months, how often has each of the following behaviors been a *problem*?	Never	Sometimes	Often
31. Angry or tearful outbursts are intense but end suddenly	N	S	O
32. Needs help from adult to stay on task	N	S	O
33. Does not notice when his/her behavior causes negative reactions	N	S	O
34. Leaves messes that others have to clean up even after instruction	N	S	O
35. Has trouble changing activities	N	S	O
36. Reacts more strongly to situations than other children	N	S	O
37. Forgets what he/she is doing in the middle of an activity	N	S	O
38. Does not realize that certain actions bother others	N	S	O
39. Gets caught up in the small details of a task or situation and misses the main idea	N	S	O
40. Has trouble "joining in" at unfamiliar social events (such as birthday parties, picnics, holiday gatherings)	N	S	O
41. Is easily overwhelmed or overstimulated by typical daily activities	N	S	O
42. Has trouble finishing tasks (such as games, puzzles, pretend play activities)	N	S	O
43. Gets out of control more than playmates	N	S	O
44. Cannot find things in room or play area even when given specific instructions	N	S	O
45. Resists change of routine, foods, places, etc.	N	S	O
46. After having a problem, will stay disappointed for a long time	N	S	O
47. Cannot stay on the same topic when talking	N	S	O
48. Talks or plays too loudly	N	S	O
49. Does not complete tasks even after given directions	N	S	O
50. Acts overwhelmed or overstimulated in crowded, busy situations (such as lots of noise, activity, or people)	N	S	O
51. Has trouble getting started on activities or tasks even after instructed	N	S	O
52. Acts too wild or out of control	N	S	O
53. Does not try as hard as his/her ability on activities	N	S	O
54. Has trouble putting the brakes on his/her actions even after being asked	N	S	O
55. Unable to finish describing an event, person, or story	N	S	O
56. Completes tasks or activities too quickly	N	S	O
57. Is unaware when he/she does well and not well	N	S	O
58. Gets easily sidetracked during activities	N	S	O
59. Has trouble remembering something, even after a brief period of time	N	S	O
60. Becomes too silly	N	S	O
61. Has a short attention span	N	S	O
62. Plays carelessly or recklessly in situations where he/she could be hurt (such as playground, swimming pool)	N	S	O
63. Is unaware when he/she performs a task right or wrong	N	S	O

BRIEF-P Preschool Scoring Summary

Date ____/____/____

Child's Name _____ Gender _____ Age _____ Relation of Rater to Child _____

Scoring Instructions

1. Remove the perforated stubs from the Rating Form and detach the answer sheet to reveal the Scoring Sheet.
2. Transfer the circled item score for each item to the box provided in that item row.
3. Sum the item scores in each column and enter the subtotal in the box at the bottom of the column.
4. Transfer the scale subtotals for Items 1-30 to the appropriate box in the row for subtotals at the bottom of the facing page.
5. Sum the two subtotals for each scale and enter the total in the Total scale raw scores box.
6. Transfer each scale raw score to the raw score column in the Scoring Summary Table below.
7. Sum the raw scores for Inhibit and Emotional Control (EC) to obtain the raw score for the Inhibitory Self-Control Index (*ISCI*).
8. Sum the raw scores for Shift and Emotional Control (EC) to obtain the raw score for the Flexibility Index (*FI*).
9. Sum the raw scores for Working Memory (WM) and Plan/Organize (PO) to obtain the raw score for the Emergent Metacognition Index (*EMI*).
10. Sum the raw scores for the five scales (Inhibit + Shift + EC + WM + PO) to obtain the raw score for the Global Executive Composite (*GEC*).
11. Locate the norms tables for the appropriate normative comparison group in the Appendix tables of the BRIEF-P Professional Manual. Find the raw score for each scale, index, and *GEC* in the raw score column and read across the row to find the corresponding *T* score and percentile. Enter the *T* score and percentile in the appropriate boxes in the Scoring Summary Table. Locate the 90% Confidence Interval (CI) value for each scale, index, and *GEC* at the bottom of the appropriate column, calculate the low end (subtract the CI value from the *T* score) and high end (add the CI value to the *T* score) of the interval, and enter those values in the spaces provided in the 90% CI column.

Scoring Summary Table

Scale/Index	Raw score	*T* score	%ile	90% CI
Inhibit				____ – ____
Shift				____ – ____
Emotional Control (EC)				____ – ____
Working Memory (WM)				____ – ____
Plan/Organize (PO)				____ – ____
ISCI (Inhibit + EC)				____ – ____
FI (Shift + EC)				____ – ____
EMI (WM + PO)				____ – ____
GEC (Inhibit + Shift + EC + WM + PO)				____ – ____

Negativity Scale

1. Negativity items are indicated with a [N] in the margin of the Scoring Sheet. For each Negativity item with a score of 3, circle that item number in the column to the right.
2. Count the number of circled item numbers to determine the **Negativity score**.
3. Using the Negativity Score table below, circle the appropriate protocol classification corresponding to that score.

Negativity score	Cumulative %	
	Parent	Teacher
0 – 2	0 – 97 Acceptable	0 – 98 Acceptable
3	98 – 99 Acceptable	99 Elevated
≥4	100 Elevated	100 Elevated

Item
30.
44.
46.
47.
53.
55.
56.
57.
59.
63.

Negativity score ____

Inconsistency Scale

For each item pair:

1. Transfer the item score for each item (marked (1) in the margin of the Scoring Sheet) to the appropriate item pairs box.
2. Subtract the ***lesser*** number from the ***greater*** number and enter the result in the *Difference* column.
3. Sum the numbers in the *Difference* column to obtain the **Inconsistency score**. Circle the appropriate protocol classification corresponding to that score in the table below.

Inconsistency score	Cumulative %	
	Parent	Teacher
0 – 6	0 – 94 Acceptable	0 – 98 Acceptable
7	97 – 98 Acceptable	99 Inconsistent
≥8	99 – 100 Inconsistent	100 Inconsistent

Item	Score	Item	Score		Difference
1.		11.		→	
3.		33.		→	
5.		45.		→	
10.		20.		→	
11.		26.		→	
16.		21.		→	
18.		52.		→	
33.		38.		→	
43.		52.		→	
48.		54.		→	

Inconsistency score ____

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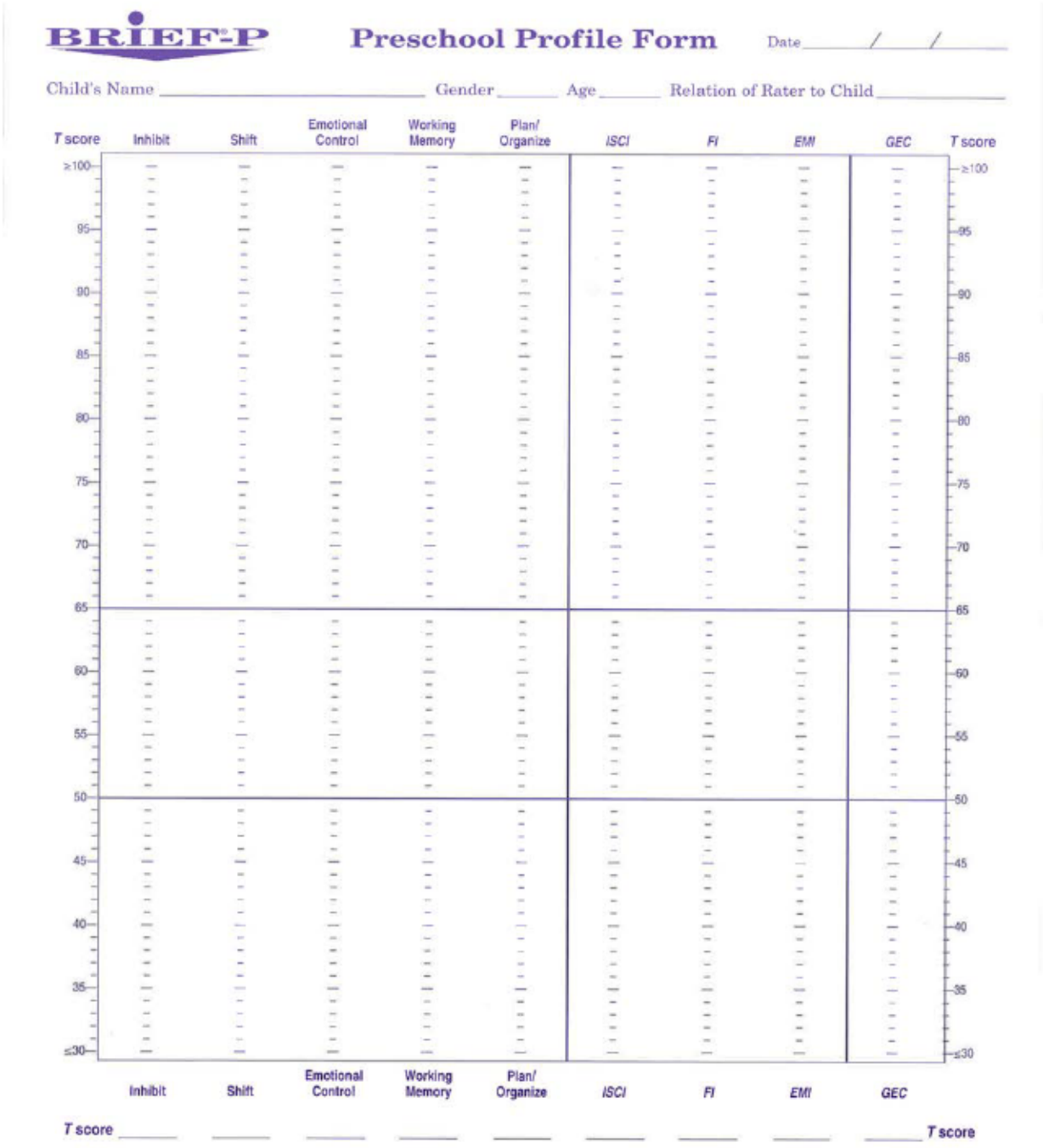
BRIEF-P
Preschool Profile Form
Date / /
Child's Name
Gender
Age
Relation of Rater to Child
T score
Inhibit
Shift
Emotional Control
Working Memory
Plan/ Organize
ISCI
FI
EMI
GEC
T score
≥100
95
90
85
80
75
70
65
60
55
50
45
40
35
≤30
Instructions: Transfer the Scale scores, Index scores, and GEC T scores from the Scoring Summary Table on the reverse side of this form. Mark an X on the tick mark corresponding to each T score. Connect the Xs (without crossing the vertical lines) to create a profile.

BRIEF®
Behavior Rating Inventory of Executive Function®
PARENT FORM

Gerard A. Gioia, PhD, Peter K. Isquith, PhD, Steven C. Guy, PhD, and Lauren Kenworthy, PhD

Instructions

On the following pages is a list of statements that describe children. We would like to know if your child has had problems with these behaviors over the past 6 months. Please answer all the items the best that you can. Please DO NOT SKIP ANY ITEMS. Think about your child as you read each statement and circle your response:

N	if the behavior is	**Never** a problem
S	if the behavior is	**Sometimes** a problem
O	if the behavior is	**Often** a problem

For example, if your child **never** has trouble completing homework on time, you would circle **N** for this item:

Has trouble completing homework on time (N) S O

If you make a mistake or want to change your answer, DO NOT ERASE. Draw an "X" through the answer you want to change, and then circle the correct answer:

Has trouble completing homework on time (X) (S) O

Before you begin answering the items, please fill in your child's name, gender, grade, age, birth date, your name, your relationship to the child, and today's date in the spaces provided at the top of the next page.

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Child's Name _____ Gender _____ Grade _____ Age _____ Birth Date ___/___/___

Your Name _____ Relationship to Child _____ Today's Date ___/___/___

	N = Never S = Sometimes O = Often			
1.	Overreacts to small problems	N	S	O
2.	When given three things to do, remembers only the first or last	N	S	O
3.	Is not a self-starter	N	S	O
4.	Leaves playroom a mess	N	S	O
5.	Resists or has trouble accepting a different way to solve a problem with schoolwork, friends, chores, etc.	N	S	O
6.	Becomes upset with new situations	N	S	O
7.	Has explosive, angry outbursts	N	S	O
8.	Tries the same approach to a problem over and over even when it does not work	N	S	O
9.	Has a short attention span	N	S	O
10.	Needs to be told to begin a task even when willing	N	S	O
11.	Does not bring home homework, assignment sheets, materials, etc.	N	S	O
12.	Acts upset by a change in plans	N	S	O
13.	Is disturbed by change of teacher or class	N	S	O
14.	Does not check work for mistakes	N	S	O
15.	Has good ideas but cannot get them on paper	N	S	O
16.	Has trouble coming up with ideas for what to do in play or free time	N	S	O
17.	Has trouble concentrating on chores, schoolwork, etc.	N	S	O
18.	Does not connect doing tonight's homework with grades	N	S	O
19.	Is easily distracted by noises, activity, sights, etc.	N	S	O
20.	Becomes tearful easily	N	S	O
21.	Makes careless errors	N	S	O
22.	Forgets to hand in homework, even when completed	N	S	O
23.	Resists change of routine, foods, places, etc.	N	S	O
24.	Has trouble with chores or tasks that have more than one step	N	S	O
25.	Has outbursts for little reason	N	S	O
26.	Mood changes frequently	N	S	O
27.	Needs help from an adult to stay on task	N	S	O
28.	Gets caught up in details and misses the big picture	N	S	O
29.	Keeps room messy	N	S	O
30.	Has trouble getting used to new situations (classes, groups, friends)	N	S	O
31.	Has poor handwriting	N	S	O
32.	Forgets what he/she was doing	N	S	O
33.	When sent to get something, forgets what he/she is supposed to get	N	S	O
34.	Is unaware of how his/her behavior affects or bothers others	N	S	O
35.	Has good ideas but does not get job done (lacks follow-through)	N	S	O
36.	Becomes overwhelmed by large assignments	N	S	O
37.	Has trouble finishing tasks (chores, homework)	N	S	O
38.	Acts wilder or sillier than others in groups (birthday parties, recess)	N	S	O
39.	Thinks too much about the same topic	N	S	O
40.	Underestimates time needed to finish tasks	N	S	O
41.	Interrupts others	N	S	O
42.	Does not notice when his/her behavior causes negative reactions	N	S	O
43.	Gets out of seat at the wrong times	N	S	O
44.	Gets out of control more than friends	N	S	O

N = Never S = Sometimes O = Often

45.	Reacts more strongly to situations than other children	N	S	O
46.	Starts assignments or chores at the last minute	N	S	O
47.	Has trouble getting started on homework or chores	N	S	O
48.	Has trouble organizing activities with friends	N	S	O
49.	Blurts things out	N	S	O
50.	Mood is easily influenced by the situation	N	S	O
51.	Does not plan ahead for school assignments	N	S	O
52.	Has poor understanding of own strengths and weaknesses	N	S	O
53.	Written work is poorly organized	N	S	O
54.	Acts too wild or "out of control"	N	S	O
55.	Has trouble putting the brakes on his/her actions	N	S	O
56.	Gets in trouble if not supervised by an adult	N	S	O
57.	Has trouble remembering things, even for a few minutes	N	S	O
58.	Has trouble carrying out the actions needed to reach goals (saving money for special item, studying to get a good grade)	N	S	O
59.	Becomes too silly	N	S	O
60.	Work is sloppy	N	S	O
61.	Does not take initiative	N	S	O
62.	Angry or tearful outbursts are intense but end suddenly	N	S	O
63.	Does not realize that certain actions bother others	N	S	O
64.	Small events trigger big reactions	N	S	O
65.	Talks at the wrong time	N	S	O
66.	Complains there is nothing to do	N	S	O
67.	Cannot find things in room or school desk	N	S	O
68.	Leaves a trail of belongings wherever he/she goes	N	S	O
69.	Leaves messes that others have to clean up	N	S	O
70.	Becomes upset too easily	N	S	O
71.	Lies around the house a lot ("couch potato")	N	S	O
72.	Has a messy closet	N	S	O
73.	Has trouble waiting for turn	N	S	O
74.	Loses lunch box, lunch money, permission slips, homework, etc.	N	S	O
75.	Cannot find clothes, glasses, shoes, toys, books, pencils, etc.	N	S	O
76.	Tests poorly even when knows correct answers	N	S	O
77.	Does not finish long-term projects	N	S	O
78.	Has to be closely supervised	N	S	O
79.	Does not think before doing	N	S	O
80.	Has trouble moving from one activity to another	N	S	O
81.	Is fidgety	N	S	O
82.	Is impulsive	N	S	O
83.	Cannot stay on the same topic when talking	N	S	O
84.	Gets stuck on one topic or activity	N	S	O
85.	Says the same things over and over	N	S	O
86.	Has trouble getting through morning routine in getting ready for school	N	S	O

BRIEF® Parent Form Scoring Summary

Date ____/____/____
Rater's Name _____

Child's Name _____ Gender _____ Grade _____ Age _____

Scoring Instructions

1. Remove the perforated stub and detach the top part of the carbonless answer sheet to reveal the scoring sheet.
2. Transfer the circled item score for each item to the box provided in that item row.
3. Sum the item scores in each column and enter the subtotal in the box at the bottom of the column.
4. Transfer the scale subtotals for Items 1-44 to the appropriate box in the row for Subtotals at the bottom of the facing page.
5. Sum the two Subtotals for each scale and enter the total in the Total Scale raw scores box beneath the scale name.
6. Transfer the Total raw score for each scale to the Raw score column in the Scoring Summary Table below.
7. Sum the raw scores for Inhibit, Shift, and Emotional Control to obtain the raw score for the Behavioral Regulation Index (*BRI*).
8. Sum the raw scores for Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor to obtain the raw score for the Metacognition Index (*MI*).
9. Sum the raw scores for the two indexes (*BRI* and *MI*) to obtain the raw score for the Global Executive Composite (*GEC*).
10. Locate the appropriate normative comparison group in the Appendix tables of the BRIEF Professional Manual. Find the raw score for each scale, index, or *GEC* in the raw score column, then move across the row to the corresponding *T* score and percentile. Enter the *T* score and percentile in the appropriate boxes in the Scoring Summary Table. Locate the Confidence Interval (CI) value for each scale, index, and *GEC* at the bottom of the appropriate column, calculate the high end (add the CI value to the *T* score) and low end (subtract the CI value from the *T* score) of the interval, and enter in the spaces provided under the heading 90% CI.

Scoring Summary Table

Scale/Index	Raw score	*T* score	%ile	90% CI
Inhibit				____–____
Shift				____–____
Emotional Control				____–____
BRI				____–____
Initiate				____–____
Working Memory				____–____
Plan/Organize				____–____
Organization of Materials				____–____
Monitor				____–____
MI				____–____
GEC (BRI + MI)				____–____

Negativity Scale

1. Locate the first Negativity item (indicated with a boxed **N** in the margin of the Scoring Sheet). For each Negativity item with a score of 3, circle that item number in the column to the right.
2. Count the number of circled items to determine the **Negativity score.**
3. Circle the appropriate Protocol classification based on that score.

Negativity score	Cumulative percentile	Protocol classification
≤4	≤90	Acceptable
5 to 6	91 – 98	Elevated
≥7	>98	Highly elevated

Item no.
8.
13.
23.
30.
62.
71.
80.
83.
85.
Negativity score (Range = 0 to 9)

Inconsistency Scale

For each item pair:

1. Transfer the item score for each item (marked (I) in the margin of the Scoring Sheet) to the appropriate item pairs box.
2. Subtract the *lesser* number from the *greater* number and enter the result in the *Difference* column.
3. Sum the numbers in the *Difference* column to obtain the **Inconsistency score.**
4. Circle the appropriate Protocol classification based on that score:

Inconsistency score	Cumulative percentile	Protocol classification
≤6	≤98	Acceptable
7 to 8	99	Questionable
≥9	>99	Inconsistent

Item no.	Score	Item no.	Score		Difference
7.		25.		→	
11.		22.		→	
27.		17.		→	
33.		32.		→	
38.		59.		→	
41.		65.		→	
42.		63.		→	
44.		54.		→	
53.		60.		→	
55.		44.		→	
				Inconsistency score (Range = 0 to 20)	

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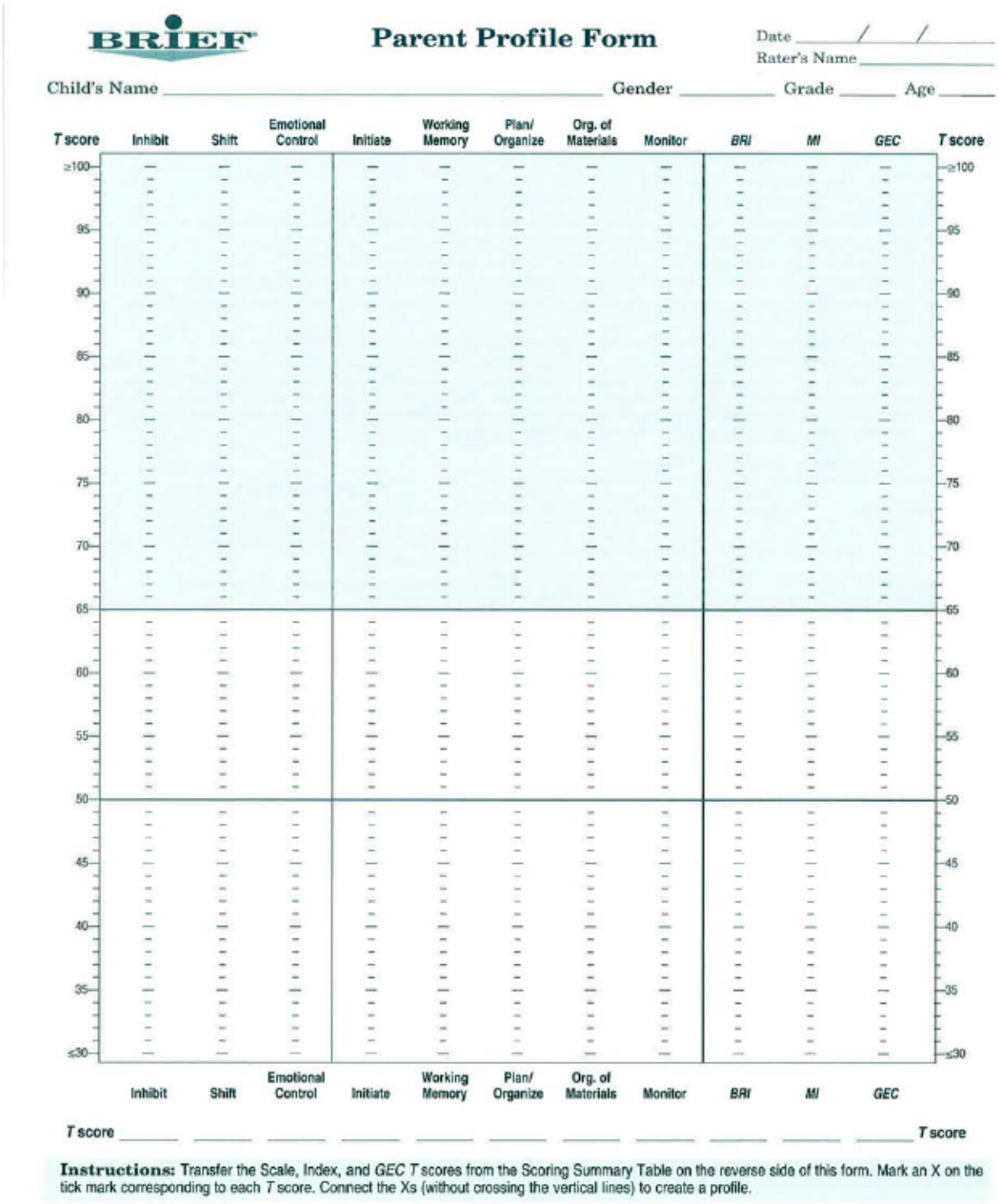


BRIEF

Parent Profile Form

Date ____/____/____
Rater's Name ____

Child's Name ____ Gender ____ Grade ____ Age ____

T score	Inhibit	Shift	Emotional Control	Initiate	Working Memory	Plan/ Organize	Org. of Materials	Monitor	BRI	MI	GEC	T score
≥100												≥100
95												95
90												90
85												85
80												80
75												75
70												70
65												65
60												60
55												55
50												50
45												45
40												40
35												35
≤30												≤30
	Inhibit	Shift	Emotional Control	Initiate	Working Memory	Plan/ Organize	Org. of Materials	Monitor	BRI	MI	GEC	
T score												T score

Instructions: Transfer the Scale, Index, and *GEC T* scores from the Scoring Summary Table on the reverse side of this form. Mark an X on the tick mark corresponding to each *T* score. Connect the Xs (without crossing the vertical lines) to create a profile.

APPENDIX 4 – QUALITY OF LIFE IN CHILDHOOD EPILEPSY SCALE

QUALITY OF LIFE IN CHILDHOOD EPILEPSY QUESTIONNAIRE

Parent Form

INSTRUCTIONS

1. This questionnaire asks about your child's day to day functioning in various life areas. It looks at how you see epilepsy affecting your child's day to day functioning. Your answers will be confidential.

2. If you choose not to participate it will not affect the care you or your child receive.

3. Please answer the questions by marking the appropriate box, like this... ☑

4. Certain questions may look alike, but each one is different. Some questions ask about problems your child may not have, but it's important for us to know this information too. Please answer each question to the best of your knowledge. Remember to answer all questions unless instructed otherwise.

5. There are no right or wrong answers. If you are unsure how to answer a question, please give the best answer you can and make a comment in the margin.

6. All comments will be read, so please feel free to make as many as you wish.

7. You may not be able to answer some questions about your child. For example, it may be difficult to tell how your child feels because s/he is too young or where disability prevents your child talking about their feelings. In such cases the "Not Applicable" response is appropriate.

SECTION 3: YOUR CHILD'S PHYSICAL ACTIVITIES

The following questions ask about physical activities your child might do.

3.1. In his/her daily activities during the past 4 weeks, how often has your child:

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
a. needed more supervision than other children his/her age?	☐	☐	☐	☐	☐	☐
b. needed special precautions (ie wearing a helmet)?	☐	☐	☐	☐	☐	☐
c. played freely in the house like other children his/her age?	☐	☐	☐	☐	☐	☐
d. played freely outside the house like other children his/her age?	☐	☐	☐	☐	☐	☐
e. gone swimming? (ie. swam independently)	☐	☐	☐	☐	☐	☐
f. participated in sports activities (other than swimming)?	☐	☐	☐	☐	☐	☐
g. stayed out overnight (with friends or family)?	☐	☐	☐	☐	☐	☐
h. played with friends away from you or your home	☐	☐	☐	☐	☐	☐
i. gone to parties without you or without supervision?	☐	☐	☐	☐	☐	☐
j. been able to do the physical activities other children his/her age do?	☐	☐	☐	☐	☐	☐

3

3.2. <u>During the past 4 weeks</u> how much of the time do you think your child:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	Not Applicable
a. felt tired	☐	☐	☐	☐	☐	☐
b. felt energetic	☐	☐	☐	☐	☐	☐

3.3 Is there anything else you would like to tell us about your child's activities?

SECTION 4: WELL-BEING

Below is a list that describes how your child might feel in general.

4.1. During the past 4 weeks, how much of the time do you think your child

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	Not applicable
a. felt down or depressed?	☐	☐	☐	☐	☐	☐
b. felt calm?	☐	☐	☐	☐	☐	☐
c. felt helpless in situations?	☐	☐	☐	☐	☐	☐
d. felt happy?	☐	☐	☐	☐	☐	☐
e. wished s/he was dead?	☐	☐	☐	☐	☐	☐
f. felt in control?	☐	☐	☐	☐	☐	☐
g. felt tense and anxious?	☐	☐	☐	☐	☐	☐
h. felt frustrated?	☐	☐	☐	☐	☐	☐
i. felt overwhelmed by events?	☐	☐	☐	☐	☐	☐
j. worried a lot?	☐	☐	☐	☐	☐	☐
k. felt confident?	☐	☐	☐	☐	☐	☐
l. felt excited or interested in something?	☐	☐	☐	☐	☐	☐
m. felt pleased about achieving something?	☐	☐	☐	☐	☐	☐
n. got easily embarrassed?	☐	☐	☐	☐	☐	☐
o. felt different or singled out?	☐	☐	☐	☐	☐	☐
p. felt nobody understood him/her?	☐	☐	☐	☐	☐	☐
q. felt valued?	☐	☐	☐	☐	☐	☐
r. felt s/he was not good at anything?	☐	☐	☐	☐	☐	☐
s. felt no one cared?	☐	☐	☐	☐	☐	☐

4.2. Is there anything else you would like to tell us about how your child feels in general?

SECTION 5: COGNITION

The following questions ask about some problems children have with concentrating, remembering, and speaking.

5.1. Compared to other children of his/her own age, how often during the past 4 weeks has your child

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
a. had difficulty attending to an activity ?	☐	☐	☐	☐	☐	☐
b. had difficulty reasoning or solving problems?	☐	☐	☐	☐	☐	☐
c. had difficulty making plans or decisions?	☐	☐	☐	☐	☐	☐
d. had difficulty keeping track of conversations?	☐	☐	☐	☐	☐	☐
e. had trouble concentrating on a task?	☐	☐	☐	☐	☐	☐
f. had difficulty concentrating on reading?	☐	☐	☐	☐	☐	☐
g. had difficulty doing one thing at a time?	☐	☐	☐	☐	☐	☐
h. reacted slowly to things being said & done?	☐	☐	☐	☐	☐	☐
i. completed activities that needed organising & planning?	☐	☐	☐	☐	☐	☐
j. found it hard remembering things?	☐	☐	☐	☐	☐	☐
k. had trouble remembering names of people?	☐	☐	☐	☐	☐	☐
l. had trouble remembering where s/he put things?	☐	☐	☐	☐	☐	☐
m. had trouble remembering things people told him/her?	☐	☐	☐	☐	☐	☐

5.1. continued: Compared to other children his/her own age, how often during the past 4 weeks has your child

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
n. had trouble remembering things s/he read hours or days before?	☐	☐	☐	☐	☐	☐
o. planned to do something then forgot?	☐	☐	☐	☐	☐	☐
p. had trouble finding the correct words?	☐	☐	☐	☐	☐	☐
q. had trouble understanding or following what others were saying?	☐	☐	☐	☐	☐	☐
r. had trouble understanding directions?	☐	☐	☐	☐	☐	☐
s. had difficulty following simple instructions?	☐	☐	☐	☐	☐	☐
t. had difficulty following complex instructions?	☐	☐	☐	☐	☐	☐
u. had trouble understanding what s/he read?	☐	☐	☐	☐	☐	☐
v. had trouble writing?	☐	☐	☐	☐	☐	☐
w. had trouble talking	☐	☐	☐	☐	☐	☐

5.2. Is there anything else you would like to tell us about your child's concentration, memory or speech?

SECTION 6: YOUR CHILD'S SOCIAL ACTIVITIES

6.1. During the past 4 weeks, how often has your child's epilepsy

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
a. limited his/her social activities (visiting friends, close relatives, or neighbours?	☐	☐	☐	☐	☐	☐
b. helped him/her to make friends?	☐	☐	☐	☐	☐	☐
c. affected his/her social interactions at school or work?	☐	☐	☐	☐	☐	☐
d. improved his/her friendships & relationships with others?	☐	☐	☐	☐	☐	☐
e. limited his/her leisure activities (hobbies or interests)?	☐	☐	☐	☐	☐	☐
f. isolated him/her from others?	☐	☐	☐	☐	☐	☐
g. improved his/her relations with family members?	☐	☐	☐	☐	☐	☐
h. made it difficult for him/her to keep friends?	☐	☐	☐	☐	☐	☐
i. frightened other people	☐	☐	☐	☐	☐	☐

6.2. During the past 4 weeks, how limited are your child's social activities compared with others his/her age because of his/her epilepsy or epilepsy-related problems?

☐	☐	☐	☐	☐
Yes, limited a lot	Yes, limited some	Yes, limited a little	Yes, but rarely	No, not limited

6.3. During the past 4 weeks, how often has your child freely discussed his/her epilepsy with friends?

☐ Very often ☐ Fairly often ☐ Sometimes ☐ Almost never ☐ Not applicable

6.4. During the past 4 weeks, how often has your child freely discussed his/her epilepsy with family?

☐ Very often ☐ Fairly often ☐ Sometimes ☐ Almost never ☐ Not applicable

6.5. Is there anything else you would like to tell us about your child's social activities?

SECTION 7: YOUR CHILD'S BEHAVIOUR

Below are statements that describe some children's behaviour.
Please answer all questions as well as you can, even if some do not seem to apply to your child.

7.1. Compared to other children his/her own age, how often during the past 4 weeks do each of the following statements describe your child?

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
a. relied on you / family to do things for him/her that s/he was able to do him/herself	☐	☐	☐	☐	☐	☐
b. asked for reassurance	☐	☐	☐	☐	☐	☐
c. was socially inappropriate (said or did something out of place in a social situation)	☐	☐	☐	☐	☐	☐
d. wanted things to be perfect	☐	☐	☐	☐	☐	☐
e. did not give up easily	☐	☐	☐	☐	☐	☐
f. angered easily	☐	☐	☐	☐	☐	☐
g. hit or attacked people	☐	☐	☐	☐	☐	☐
h. swore in public	☐	☐	☐	☐	☐	☐
i. joined in activities with other children	☐	☐	☐	☐	☐	☐
j. feared unfamiliar places, situations or people	☐	☐	☐	☐	☐	☐
k. preferred his/her own company instead of seeking out others	☐	☐	☐	☐	☐	☐
l. was obedient	☐	☐	☐	☐	☐	☐
m. set high standards for self	☐	☐	☐	☐	☐	☐
n. did not worry about what others thought	☐	☐	☐	☐	☐	☐
o. got along with other children	☐	☐	☐	☐	☐	☐
p. wished s/he was someone or somewhere else	☐	☐	☐	☐	☐	☐

7.1 continued: Compared to other children his/her own age, how often during the past 4 weeks do each of the following statements describe your child?

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
q. acted without thinking	☐	☐	☐	☐	☐	☐
r. demanded a lot of attention	☐	☐	☐	☐	☐	☐
s. was decisive	☐	☐	☐	☐	☐	☐
t. was independent	☐	☐	☐	☐	☐	☐
u. preferred routines or disliked changes	☐	☐	☐	☐	☐	☐
v. did things just to prove s/he could	☐	☐	☐	☐	☐	☐
w. preferred the company of adults	☐	☐	☐	☐	☐	☐

7.2. Is there anything else you would like to tell us about your child's behaviour?

SECTION 8: GENERAL HEALTH

8.1. Compared to other children his/her age , how good do you think your child's health has been in the past 4 weeks? Please consider your child's epilepsy as part of his/her health when you answer this question.

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

8.2. Is there anything else you would like to tell us about how epilepsy has affected your child's health?

SECTION 9: QUALITY OF LIFE

9.1. In the past 4 weeks what has your child's quality of life been?

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

10.0 This questionnaire was completed by the child's

☐ mother
☐ father
☐ both parents
☐ other carers

If you would like a copy of any publications arising from this study, please complete the detachable sheet following. Thank you for your participation.

Request for copy of any publications arising from this study

Your Name .....

Your Child's Name .....

Your Address .....

.....

.....

APPENDIX 5 – TANNER STAGING

The Tanner Stages

Because the onset and progression of puberty are so variable, Tanner has proposed a scale, now uniformly accepted, to describe the onset and progression of pubertal changes (Fig. 9-24). Boys and girls are rated on a 5 point scale. Boys are rated for genital development and pubic hair growth, and girls are rated for breast development and pubic hair growth.

Pubic hair growth in females is staged as follows (Fig 9-24, B):

- **Stage I (Preadolescent)** - Vellos hair develops over the pubes in a manner not greater than that over the anterior wall. There is no sexual hair.
- **Stage II** - Sparse, long, pigmented, downy hair, which is straight or only slightly curled, appears. These hairs are seen mainly along the labia. This stage is difficult to quantitate on black and white photographs, particularly when pictures are of fair-haired subjects.
- **Stage III** - Considerably darker, coarser, and curlier sexual hair appears. The hair has now spread sparsely over the junction of the pubes.
- **Stage IV** - The hair distribution is adult in type but decreased in total quantity. There is no spread to the medial surface of the thighs.
- **Stage V** - Hair is adult in quantity and type and appears to have an inverse triangle of the classically feminine type. There is spread to the medial surface of the thighs but not above the base of the inverse triangle.

The stages in male pubic hair development are as follows (Fig. 9-24, B):

- **Stage I (Preadolescent)** - Vellos hair appears over the pubes with a degree of development similar to that over the abdominal wall. There is no androgen-sensitive pubic hair.
- **Stage II** - There is sparse development of long pigmented downy hair, which is only slightly curled or straight. The hair is seen chiefly at the base of penis. This stage may be difficult to evaluate on a photograph, especially if the subject has fair hair.
- **Stage III** - The pubic hair is considerably darker, coarser, and curlier. The distribution is now spread over the junction of the pubes, and at this point that hair may be recognized easily on black and white photographs.
- **Stage IV** - The hair distribution is now adult in type but still is considerably less that seen in adults. There is no spread to the medial surface of the thighs.
- **Stage V** - Hair distribution is adult in quantity and type and is described in the inverse triangle. There can be spread to the medial surface of the thighs.

In young women, the Tanner stages for breast development are as follows (Fig. 9-24, C):

- **Stage I (Preadolescent)** - Only the papilla is elevated above the level of the chest wall.
- **Stage II - (Breast Budding)** - Elevation of the breasts and papillae may occur as small mounds along with some increased diameter of the areolae.
- **Stage III** - The breasts and areolae continue to enlarge, although they show no separation of contour.
- **Stage IV** - The areolae and papillae elevate above the level of the breasts and form secondary mounds with further development of the overall breast tissue.
- **Stage V** - Mature female breasts have developed. The papillae may extend slightly above the contour of the breasts as the result of the recession of the aerolae.

The stages for male genitalia development are as follows: (Fig. 9-24, A):

- **Stage I (Preadolescent)**- The testes, scrotal sac, and penis have a size and proportion similar to those seen in early childhood.
- **Stage II** - There is enlargement of the scrotum and testes and a change in the texture of the scrotal skin. The scrotal skin may also be reddened, a finding not obvious when viewed on a black and white photograph.
- **Stage III** - Further growth of the penis has occurred, initially in length, although with some increase in circumference. There also is increased growth of the testes and scrotum.
- **Stage IV** - The penis is significantly enlarged in length and circumference, with further development of the glans penis. The testes and scrotum continue to enlarge, and there is distinct darkening of the scrotal skin. This is difficult to evaluate on a black-and-white photograph.
- **Stage V** - The genitalia are adult with regard to size and shape.

Source:
Reprinted with permission from Feingold, David. "Pediatric Endocrinology" In *Atlas of Pediatric Physical Diagnosis, Second Edition*, Philadelphia, W.B. Saunders, 1992, 9.16-19

APPENDIX 6 – PEDSQL

ID#_____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **TEENS** (ages 13-18)

DIRECTIONS

On the following page is a list of things that might be a problem for **your teen**. Please tell us **how much of a problem** each one has been for **your teen** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your teen had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **CHILDREN** (ages **8-12**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **YOUNG CHILDREN** (ages **5-7**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other kids not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

Please complete this section if your child attends school or daycare

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Doing the same school activities as peers	0	1	2	3	4
2. Missing school/daycare because of not feeling well	0	1	2	3	4
3. Missing school/daycare to go to the doctor or hospital	0	1	2	3	4

ID#_____

Date:_____

PedsQL™

Family Impact Module

Version 2.0

PARENT REPORT

DIRECTIONS

Families of children sometimes have special concerns or difficulties because of the child's health. On the following page is a list of things that might be a problem for **you**. Please tell us **how much of a problem** each one has been for **you** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, as a result of your child's health, how much of a problem have **you** had with…*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel tired during the day	0	1	2	3	4
2. I feel tired when I wake up in the morning	0	1	2	3	4
3. I feel too tired to do the things I like to do	0	1	2	3	4
4. I get headaches	0	1	2	3	4
5. I feel physically weak	0	1	2	3	4
6. I feel sick to my stomach	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel anxious	0	1	2	3	4
2. I feel sad	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I feel frustrated	0	1	2	3	4
5. I feel helpless or hopeless	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel isolated from others	0	1	2	3	4
2. I have trouble getting support from others	0	1	2	3	4
3. It is hard to find time for social activities	0	1	2	3	4
4. I do not have enough energy for social activities	0	1	2	3	4

COGNITIVE FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4

COMMUNICATION *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel that others do not understand my family's situation	0	1	2	3	4
2. It is hard for me to talk about my child's health with others	0	1	2	3	4
3. It is hard for me to tell doctors and nurses how I feel	0	1	2	3	4

PedsQL 3

*In the past **ONE month**, as a result of your child's health, how much of a problem have **you** had with…*

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I worry about whether or not my child's medical treatments are working	0	1	2	3	4
2. I worry about the side effects of my child's medications/medical treatments	0	1	2	3	4
3. I worry about how others will react to my child's condition	0	1	2	3	4
4. I worry about how my child's illness is affecting other family members	0	1	2	3	4
5. I worry about my child's future	0	1	2	3	4

DIRECTIONS

Below is a list of things that might be a problem for **your family**. Please tell us **how much of a problem** each one has been for **your family** during the **past ONE month.**

*In the past **ONE month**, as a result of your child's health, how much of a problem has **your family** had with…*

DAILY ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Family activities taking more time and effort	0	1	2	3	4
2. Difficulty finding time to finish household tasks	0	1	2	3	4
3. Feeling too tired to finish household tasks	0	1	2	3	4

FAMILY RELATIONSHIPS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Lack of communication between family members	0	1	2	3	4
2. Conflicts between family members	0	1	2	3	4
3. Difficulty making decisions together as a family	0	1	2	3	4
4. Difficulty solving family problems together	0	1	2	3	4
5. Stress or tension between family members	0	1	2	3	4

APPENDIX 7 – EQ-5D-5L QUESTIONNAIRE

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

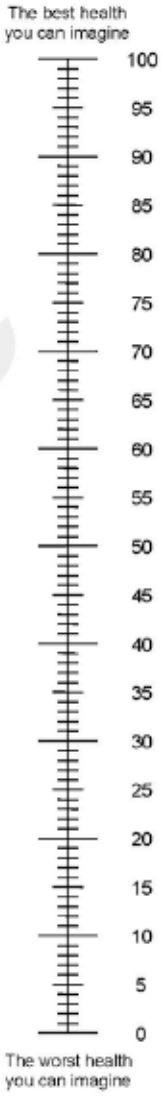
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 8 – KAROLINSKA SLEEPINESS SCALE

Here are some descriptors about how alert or sleepy you might be feeling right now. Please read the carefully and CIRCLE the number that best corresponds to the statement decribing how you feel at the moment.

1. Extremely alert
2. Very Alert
3. Alert
4. Rather Alert
5. Neither alert nor sleepy
6. Some signs of sleepiness
7. Sleepy, but no difficulty remaining awake
8. Sleepy,with some effort to keep alert
9. Extremely sleepy, fighting sleep

APPENDIX 9 – MAXIMUM ALLOWABLE BLOOD DRAW VOLUMES

Seattle Children's
HOSPITAL · RESEARCH · FOUNDATION

Maximum allowable blood draw volumes:

PATIENT'S WEIGHT		TOTAL VOLUME	MAXIMUM mL IN ONE BLOOD DRAW	MAXIMUM mL IN A 30-DAY PERIOD
Kg	lbs	mL	2.5% of total blood vol	5% of total blood vol
1	2.2	100	2.5	5
2	4.4	200	5	10
3	3.3	240	6	12
4	8.8	320	8	16
5	11	400	10	20
6	13.2	480	12	24
7	15.4	560	14	28
8	17.6	640	16	32
9	19.8	720	18	36
10	22	800	20	40
11 thru 15	24 thru 33	880-1200	22-30	44-60
16 thru 20	35 thru 44	1280-1600	32-40	64-80
21 thru 25	46 thru 55	1680-2000	42-50	64-100
26 thru 30	57 thru 66	2080-2400	52-60	104-120
31 thru 35	68 thru 77	2480-2800	62-70	124-140
36 thru 40	79 thru 88	2880-3200	72-80	144-160
41 thru 45	90 thru 99	3280-3600	82-90	164-180
46 thru 50	101 thru 110	3680-4000	92-100	184-200
51 thru 55	112 thru 121	4080-4400	102-110	204-220
56 thru 60	123 thru 132	4480-4800	112-120	224-240
61 thru 65	134 thru 143	4880-5200	122-130	244-260
66 thru 70	145 thru 154	5280-5600	132-140	264-280
71 thru 75	156 thru 165	5680-6000	142-150	284-300
76 thru 80	167 thru 176	6080-6400	152-160	304-360
81 thru 85	178 thru 187	6480-6800	162-170	324-340
86 thru 90	189 thru 198	6880-7200	172-180	344-360
91 thru 95	200 thru 209	7280-7600	182-190	364-380
96 thru 100	211 thru 220	7680-8000	192-200	384-400

Based on blood volume of:
1 to 2 kg 100 mL/kg (pre-term infant)
>2 kg 80 mL/kg (term infant - adult)
This information is similar to that used by the Committee on Clinical Investigations at Children's Hospital in Los Angeles, and at Baylor College of Medicine in Dallas, TX.

Adapted by Rhona Jack, Ph.D. August 2001
Children's Hospital and Regional Medical Center Laboratory
Seattle, WA

APPENDIX 10 – SUMMARY OF PROTOCOL AMENDMENT ~~2.3.8~~3.3

Summary of Changes from Amendment 2.3.8 to Amendment 3.3 of the protocol.

The protocol amendment number was updated to Amendment 3.3, 2 February 2018.

Rationale: Increase n of Cohort 2 based on results from Study 1 which show that the SD can range between 50% and 69%.	
Original Text	**Amendment Text**
Synopsis and Section 3.2, 4.7 Approximately 85 subjects will be screened to obtain 80 subjects who enter the Baseline Period. Of these 80 subjects, it is estimated that at least 70 subjects will be randomized into the Titration Period.	Synopsis and Section 3.2, 4.7 Approximately **115** subjects will be screened to ~~obtain 80 subjects who enter the Baseline Period. Of these 80 subjects, it is estimated that at least 70~~ **randomize approximately 90** subjects~~ will be randomized into the Titration Period~~.
Synopsis and Section 3.2 Approximately 25 subjects will be screened to ensure 20 subjects enter the study and complete all PK assessments. Subjects who discontinue prior to completion of all study-related procedures may be replaced.	Synopsis and Section 3.2 Approximately 25 subjects will be screened to ensure **18-20** subjects enter the study and complete all PK assessments. Subjects who discontinue prior to completion of all study-related procedures may be replaced.
Rationale: Increase n of Cohort 2 based on results from Study 1 which show that the SD can range between 50% and 69%.	
Original Text	**Amendment Text**
Synopsis and Section 10.1: The sample size for Cohort 2 is based on results from the only randomized, placebo-controlled studies in subjects with Dravet syndrome can be found in the European Public Assessment Report (EPAR) for STP (EMA 2007). The EPAR summarizes the results from two studies: STICLO France and STICLO Italy. In the STP groups, the standard deviation (SD) of the percentage change in seizure frequency from baseline to Month 2 was 42% in the French trial and 26% in the Italian trial. The analogous SDs for placebo groups were 38% and 62%. An SD of 50% was assumed for the primary analysis in this trial comparing ZX008 to placebo on the change from baseline in seizure frequency. Using a two-sided test at the α=0.05 significance level, a sample size of 35 subjects per treatment group affords 90% power to detect a difference in mean change from baseline of 40 percentage points. Thus, the total sample size for Cohort 2 is planned to be 70 subjects (35 per arm).	Synopsis and Section 10,1: The sample size for Cohort 2 is based on results from **Study 1,** the ~~only~~ randomized, placebo-controlled ~~studies~~**study** in subjects with Dravet syndrome **sponsored by Zogenix (Lagae 2017).** ~~can be found in the European Public Assessment Report (EPAR) for STP (EMA 2007). The EPAR summarizes the results from two studies: STICLO France and STICLO Italy. In the STP groups, t~~**The** standard deviation (SD) of the percentage change in seizure frequency from baseline to ~~Month 2 was 42% in the French trial and 26% in the Italian trial. The analogous SDs for placebo groups were 38% and 62%. An SD of 50% was assumed for the primary analysis in this trial comparing ZX008 to placebo on the change from baseline in seizure frequency. U~~ **the end of study (Day 99) was 50% for the 0.8 mg/kg/day group and 69% for the 0.2 mg/kg/day group. For the sample size calculation for Cohort 2, the SD is assumed to be intermediate between the SDs observed in the high and low dose groups in Study 1. Assuming an SD of 58 and** using a two-sided test at the α=0.05 significance level, a sample size of ~~35~~**45** subjects per treatment group affords 90% power to detect a difference in mean change **in**

	seizure frequency from baseline of 40 percentage points. Thus, the total sample size for Cohort 2 is planned to be ~~70~~**approximately 90** subjects (~~35~~**45** per arm).
Synopsis and Section 10.1: The 20 subjects targeted for the PK phase of the study is expected to be sufficient to allow for the extension of the PK information gained in the ongoing PK study in adults and existing PBPK models to pediatric patients with Dravet syndrome.	Synopsis and Section 10.1: The **18-20** subjects targeted for the PK phase of the study is expected to be sufficient to allow for the extension of the PK information gained in the ongoing PK study in adults and existing PBPK models to pediatric patients with Dravet syndrome.

Rationale: Updating Statistical Analysis and efficacy objectives to align with Statistical Analysis Plan: Moving CGI from exploratory to secondary objectives, removing 40% decrease in seizure frequency and adding 50% decrease in seizure frequency to secondary objectives

Original Text	**Amendment Text**
Synopsis and Section 2.2 The key secondary efficacy objectives of the study are related to Cohort 2 and include: o To demonstrate that ZX008 is superior to placebo on the following endpoints: – The proportion of subjects who achieve a ≥ 40% reduction from baseline in convulsive seizure frequency. – The proportion of subjects who achieve a ≥ 50% reduction from baseline in convulsive seizure frequency. – The longest convulsive seizure-free interval.	Synopsis and Section 2.2 The key secondary efficacy objectives of the study are related to Cohort 2 and include: o To demonstrate that ZX008 is superior to placebo on the following endpoints: ~~– The proportion of subjects who achieve a ≥ 40% reduction from baseline in convulsive seizure frequency.~~ – The proportion of subjects who achieve a ≥ 50% reduction from baseline in convulsive seizure frequency. – The longest convulsive seizure-free interval.

Synopsis and Section 2.3 Additional secondary efficacy objectives of the study (Cohort 2) are: o To demonstrate that ZX008 is superior to placebo on the following endpoints: – The number of convulsive seizure-free days. – The proportion of subjects who achieve ≥ 75% reductions from baseline in convulsive seizure frequency. – The change from baseline in non-convulsive seizure frequency. – The change from baseline in convulsive + non-convulsive seizure frequency. – The incidence of rescue medication usage. – The incidence of hospitalization to treat seizures. – The incidence of status epilepticus (SE). – The change from baseline in health-related quality of life (HRQOL) measured using the Pediatric Quality of Life Inventory™ (PedsQL) Generic Core Scale. – The change from baseline in PedsQL Family Impact module score. – Change from baseline in subjects' quality of life measured using the Quality of Life in Childhood Epilepsy (QOLCE) – The change from baseline in the HRQOL of the parent/caregiver using the standardized measure of health status (EQ-5D-5L) scale. – The change from baseline on the impacts of the condition on parents and the family using the PedsQL family impact module.	Synopsis and Section 2.3 Additional secondary efficacy objectives of the study (Cohort 2) are: o To demonstrate that ZX008 is superior to placebo on the following endpoints: – The number of convulsive seizure-free days. – The proportion of subjects who achieve ≥ **25% or** ≥ 75% reductions from baseline in convulsive seizure frequency. – The change from baseline in non-convulsive seizure frequency. – The change from baseline in convulsive + non-convulsive seizure frequency. – The incidence of rescue medication usage. – The incidence of hospitalization to treat seizures. – The incidence of status epilepticus (SE). – The change from baseline in health-related quality of life (HRQOL) measured using the Pediatric Quality of Life Inventory™ (PedsQL) Generic Core Scale. – The change from baseline in PedsQL Family Impact module score. – Change from baseline in subjects' quality of life measured using the Quality of Life in Childhood Epilepsy (QOLCE) – The change from baseline in the HRQOL of the parent/caregiver using the standardized measure of health status (EQ-5D-5L) scale. – The change from baseline on the impacts of the condition on parents and the family using the PedsQL family impact module. – **Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the principal investigator.** – **CGI-I rating, as assessed by the parent/caregiver.**
Synopsis and Section 2.4 Exploratory objectives of this study (Cohort 2) include: – To assess the change from baseline in health and social care resource use. These measures include planned and unplanned hospital visits, use of ambulances, general practitioner (GP) visits, speech and language therapy utilization, occupational and physical therapy utilization. – Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the principal investigator.	Synopsis and Section 2.4 Exploratory objectives of this study (Cohort 2) include: – To assess the change from baseline in health and social care resource use. These measures include planned and unplanned hospital visits, use of ambulances, general practitioner (GP) visits, speech and language therapy utilization, occupational and physical therapy utilization. – ~~Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the principal investigator.~~

– CGI-I rating, as assessed by the parent/caregiver. – Change from baseline in sleep quality. – Change from baseline in mealtime behavior.	~~– CGI-I rating, as assessed by the parent/caregiver.~~ – Change from baseline in sleep quality. – Change from baseline in mealtime behavior.
Section 10.5.1.1 Primary Efficacy Analysis – Cohort 2 The first key secondary endpoint – the proportion of subjects who achieve a ≥ 40% reduction from baseline in convulsive seizure frequency – is derived directly from the primary endpoint. That is, the proportion of subjects in the ZX008 group who have a change in convulsive frequency of at least 40 percentage points will be compared to the analogous proportion in the placebo group. The comparison will be made using a logistic regression model that incorporates the same factors and covariates as the ANCOVA used in the primary analysis. The second secondary endpoint, the proportion achieving a > 50% reduction in convulsive seizures, will be analyzed similarly. The analyses will be performed using data collected over the T + M period. The longest interval between convulsive seizures will be calculated for each subject over the entire T + M period. The ZX008 and placebo groups will be compared using a log rank test.	**Section 10.5.1.1 Primary Efficacy Analysis – Cohort 2** The first key secondary endpoint – the proportion of subjects who achieve a ≥ **50%** reduction from baseline in convulsive seizure frequency – is derived directly from the primary endpoint. That is, the proportion of subjects in the ZX008 group who have a change in convulsive frequency of at least **50** percentage points will be compared to the analogous proportion in the placebo group. The comparison will be made using a logistic regression model that incorporates the same factors and covariates as the ANCOVA used in the primary analysis. ~~The second secondary endpoint, the proportion achieving a > 50% reduction in convulsive seizures, will be analyzed similarly.~~ The analyses will be performed using data collected over the T + M period. The longest interval between convulsive seizures will be calculated for each subject over the entire T + M period. The ZX008 and placebo groups will be compared using a Wilcoxon test.
Section 10.4.1.3 Multiplicity Strategy and Testing Hierarchy – Cohort 2 The efficacy analyses will employ a serial gatekeeper strategy to maintain the Type 1 error rate at α=0.05 across the family of analyses that support the primary and key secondary objectives. The strategy specifies a hierarchy of significance tests where each test acts as a gatekeeper to the tests below it. The primary and key secondary endpoints will be assessed in the following order entailing comparisons between the ZX008 and placebo groups on • The change in MCSF from baseline. • The proportion of subjects who achieve a ≥ 40% reduction from baseline in convulsive seizure frequency.	**Section 10.4.1.3 Multiplicity Strategy and Testing Hierarchy – Cohort 2** The efficacy analyses will employ a serial gatekeeper strategy to maintain the Type 1 error rate at α=0.05 across the family of analyses that support the primary and key secondary objectives. The strategy specifies a hierarchy of significance tests where each test acts as a gatekeeper to the tests below it. The primary and key secondary endpoints will be assessed in the following order entailing comparisons between the ZX008 and placebo groups on • The change in MCSF from baseline. • ~~The proportion of subjects who achieve a ≥ 40% reduction from baseline in convulsive seizure frequency.~~

• The proportion of subjects who achieve a ≥ 50% reduction from baseline in convulsive seizure frequency. • The longest convulsive seizure-free interval.	• The proportion of subjects who achieve a ≥ 50% reduction from baseline in convulsive seizure frequency. • The longest convulsive seizure-free interval.
Section 10.5.2 Safety Analyses Hematology and chemistry laboratory results for subjects in Cohort 2 will be summarized using shift tables that tabulate the proportion of subjects who have lab results that change from baseline. Shift tables will be presented for each time point where lab results are collected by descriptive statistics at each time point available. Mean change from baseline will also be calculated for continuous hematology and chemistry results at all time points available.	**Section 10.5.2 Safety Analyses** Hematology and chemistry laboratory results for subjects in Cohort 2 will be summarized ~~using shift tables that tabulate the proportion of subjects who have lab results that change from baseline. Shift tables will be presented for each time point where lab results are collected~~ **by descriptive statistics at each time point available**. Mean change from baseline will also be calculated for continuous hematology and chemistry results at all time points available.

Rationale: Updates to Table 15, Adverse Events of Special Interest

Original Text	**Amendment Text**
Table 14 Adverse Events of Special Interest	**Table 14 Adverse Events of Special Interest**

CV/Respiratory	~~**CV/Respiratory**~~
1. Chest pain – any pain in sternal area that is described for example as crushing, burning, sharp, stabbing or dull.	~~1. Chest pain – any pain in sternal area that is described for example as crushing, burning, sharp, stabbing or dull.~~
2. Dyspnea/shortness of breath – any signs of difficult or labored breathing unrelated to a previous medical condition that has not worsened.	~~2. Dyspnea/shortness of breath – any signs of difficult or labored breathing unrelated to a previous medical condition that has not worsened.~~
3. Persistent cough – longer than 4 weeks without a confirmed identified pathogen (or any other persistent cough that the investigator feels is suspicious).	~~3. Persistent cough – longer than 4 weeks without a confirmed identified pathogen (or any other persistent cough that the investigator feels is suspicious).~~

4. Increase in blood pressure >30% from Screening blood pressure or systolic pressure ≥140 mmHg or diastolic pressure ≥90mmHg after repeated measures during one visit (Only if the repeat measures in triplicate confirm the finding, and in the Investigator's opinion the finding is not due to the subject's agitation of non-cooperation, should this be reported as an AESI). Blood pressure should be repeated at appropriate times within the visit.	~~4. Increase in blood pressure >30% from Screening blood pressure or systolic pressure ≥140 mmHg or diastolic pressure ≥90mmHg after repeated measures during one visit (Only if the repeat measures in triplicate confirm the finding, and in the Investigator's opinion the finding is not due to the subject's agitation of non-cooperation, should this be reported as an AESI). Blood pressure should be repeated at appropriate times within the visit.~~
5. New onset heart murmur	~~5. New onset heart murmur~~
6. Tachycardia – a persistent HR >30% above the screening value and unrelated to exercise, exertion or anxiety. (Only if the repeat measures in triplicate confirm the finding, and in the Investigator's opinion the finding is not due to the subject's agitation of non-cooperation, should this be reported as an AESI). Heart rate should be repeated at appropriate times within the visit.	~~6. Tachycardia – a persistent HR >30% above the screening value and unrelated to exercise, exertion or anxiety. (Only if the repeat measures in triplicate confirm the finding, and in the Investigator's opinion the finding is not due to the subject's agitation of non-cooperation, should this be reported as an AESI). Heart rate should be repeated at appropriate times within the visit.~~
7. Bradycardia – a persistent HR <50 bpm. (Only if the repeat measures in triplicate confirm the finding, and in the Investigator's opinion the finding is not due to the subject's agitation of non-cooperation, should this be reported as an AESI)Heart rate should be repeated at appropriate times within the visit.	~~7. Bradycardia – a persistent HR <50 bpm. (Only if the repeat measures in triplicate confirm the finding, and in the Investigator's opinion the finding is not due to the subject's agitation of non-cooperation, should this be reported as an AESI)Heart rate should be repeated at appropriate times within the visit.~~
8. Signs that could indicate right ventricular failure: □ Peripheral edema □ Ascites □ Syncope □ Decompensated right ventricular failure – symptoms include shortness of breath, frequent coughing especially when lying flat, abdominal swelling and pain, dizziness, fainting, and fatigue	~~8. Signs that could indicate right ventricular failure:~~ ~~□ Peripheral edema~~ ~~□ Ascites~~ ~~□ Syncope~~ ~~□ Decompensated right ventricular failure – symptoms include shortness of breath, frequent coughing especially when lying flat, abdominal swelling and pain, dizziness, fainting, and fatigue~~

9. Signs on ECHO indicative of potential valvulopathy (≤18 years of age) □ Valve regurgitation (aortic or mitral) □ Moderate or severe valve regurgitation (tricuspid or pulmonary) □ Mean Mitral valve gradient ≥ 4 mmHg □ Mean Aortic valve gradient ≥ 15 mmHg □ Mean Tricuspid valve gradient ≥ 4 mmHg □ Peak Pulmonary valve gradient ≥ 21 mmHg	~~9. Signs on ECHO indicative of potential valvulopathy (≤18 years of age)~~ ~~□ Valve regurgitation (aortic or mitral)~~ ~~□ Moderate or severe valve regurgitation (tricuspid or pulmonary)~~ ~~□ Mean Mitral valve gradient ≥ 4 mmHg~~ ~~□ Mean Aortic valve gradient ≥ 15 mmHg~~ ~~□ Mean Tricuspid valve gradient ≥ 4 mmHg~~ ~~□ Peak Pulmonary valve gradient ≥ 21 mmHg~~
10. Signs on ECHO indicative of potential valvulopathy (>18 years of age) □ Mild or greater severity valve regurgitation (aortic or mitral) □ Moderate or severe valve regurgitation (tricuspid or pulmonary) □ Mean Diatolic Mitral valve gradient ≥ 4 mmHg □ Mean Systolic Aortic valve gradient ≥ 15 mmHg □ Mean Diastolic Tricuspid valve gradient ≥ 4 mmHg □ Peak Systolic Pulmonary valve gradient ≥ 21 mmHg	~~10. Signs on ECHO indicative of potential valvulopathy (>18 years of age)~~ ~~□ Mild or greater severity valve regurgitation (aortic or mitral)~~ ~~□ Moderate or severe valve regurgitation (tricuspid or pulmonary)~~ ~~□ Mean Diatolic Mitral valve gradient ≥ 4 mmHg~~ ~~□ Mean Systolic Aortic valve gradient ≥ 15 mmHg~~ ~~□ Mean Diastolic Tricuspid valve gradient ≥ 4 mmHg~~ ~~□ Peak Systolic Pulmonary valve gradient ≥ 21 mmHg~~
11. Signs on ECHO indicative of pulmonary hypertension (≤18 years of age) a. Tricuspid Regurgitation Jet velocity > 2.8 m/s with or without the following findings, OR b. One of the following findings in the absence of being able to measure Tricuspid Regurgitation Jet velocity: i. Change in right ventricle/left ventricle basal diameter ratio > 1.0 ii. Right ventricular acceleration time < 100 msec	~~11. Signs on ECHO indicative of pulmonary hypertension (≤18 years of age)~~ ~~a. Tricuspid Regurgitation Jet velocity > 2.8 m/s with or without the following findings, OR~~ ~~b. One of the following findings in the absence of being able to measure Tricuspid Regurgitation Jet velocity:~~ ~~i. Change in right ventricle/left ventricle basal diameter ratio > 1.0~~ ~~ii. Right ventricular acceleration time < 100 msec~~

iii. Dilatation of the inferior vena cava (diameter>21 mm and <50% inspiratory decrease) and/or right atrium iv. Change in the geometry of the interventricular septum in systole (flattening) with left ventricular eccentricity index >1.1 in systole and/or in diastole v. Early diastolic pulmonary regurgitation velocity > 2.2 m/s vi. Tricuspid Annular Plane Systolic Excursion below 18 mm or below Z-score −2	~~iii. Dilatation of the inferior vena cava (diameter>21 mm and <50% inspiratory decrease) and/or right atrium~~ ~~iv. Change in the geometry of the interventricular septum in systole (flattening) with left ventricular eccentricity index >1.1 in systole and/or in diastole~~ ~~v. Early diastolic pulmonary regurgitation velocity > 2.2 m/s~~ vi. ~~Tricuspid Annular Plane Systolic Excursion below 18 mm or below Z-score −2~~
12. Signs on ECHO indicative of pulmonary hypertension (>18 years of age) a. Tricuspid Regurgitation Jet velocity > 2.8 m/s with or without the following findings, OR b. One of the following findings in the absence of being able to measure Tricuspid Regurgitation Jet velocity: vii. Change in right ventricle/left ventricle basal diameter ratio > 1.0 viii. Right ventricular outflow tract flow acceleration time < 100 msec ix. Dilatation of the inferior vena cava (diameter>21 mm and <50% inspiratory collapse) and/or right atrial dilatation x. Change in the geometry of the interventricular septum in systole (flattening) with left ventricular eccentricity index >1.1 in systole and/or in diastole xi. Early diastolic pulmonary regurgitation flow velocity > 2.2 m/s xii. Tricuspid Annular Plane Systolic Excursion below 18 mm	12. ~~Signs on ECHO indicative of pulmonary hypertension (>18 years of age)~~ ~~a. Tricuspid Regurgitation Jet velocity > 2.8 m/s with or without the following findings, OR~~ ~~b. One of the following findings in the absence of being able to measure Tricuspid Regurgitation Jet velocity:~~ ~~vii. Change in right ventricle/left ventricle basal diameter ratio > 1.0~~ ~~viii. Right ventricular outflow tract flow acceleration time < 100 msec~~ ~~ix. Dilatation of the inferior vena cava (diameter>21 mm and <50% inspiratory collapse) and/or right atrial dilatation~~ ~~x. Change in the geometry of the interventricular septum in systole (flattening) with left ventricular eccentricity index >1.1 in systole and/or in diastole~~ ~~xi. Early diastolic pulmonary regurgitation flow velocity > 2.2 m/s~~ xii. ~~Tricuspid Annular Plane Systolic Excursion below 18 mm~~

Metabolic/Endocrine 1. Elevated prolactin level ≥2x above the upper limit of normal (ULN) 2. Galactorrhea 3. Gynecomastia 4. Increase in fasting serum blood glucose ≥2x ULN 5. Hypoglycemia – <3.0 mmol/l or 54 mg/dl, whether that level is associated with symptoms or not	**Metabolic/Endocrine** 1. Elevated prolactin level ≥2x above the upper limit of normal (ULN) ~~2. Galactorrhea~~ ~~3. Gynecomastia~~ ~~4. Increase in fasting serum blood glucose ≥2x ULN~~ ~~5~~ 2. Hypoglycemia – <3.0 mmol/l or 54 mg/dl, whether that level is associated with symptoms or not
Neuropsychiatric 1. Serotonin syndrome (At least 3 of following symptoms must be present: Agitation, restlessness, confusion, both increased HR and blood pressure, dilated pupils, muscle twitching, muscle rigidity, hyperhidrosis, diarrhea, headache, shivering, tremors, both nausea and vomiting) 2. Hallucinations 3. Psychosis 4. Euphoria 5. Mood disorders: depression and anxiety if they rise to a level of a disorder 6. Suicidal thoughts, ideation or gestures	**Neuropsychiatric** ~~1. Serotonin syndrome (At least 3 of following symptoms must be present: Agitation, restlessness, confusion, both increased HR and blood pressure, dilated pupils, muscle twitching, muscle rigidity, hyperhidrosis, diarrhea, headache, shivering, tremors, both nausea and vomiting)~~ ~~2. Hallucinations~~ ~~3. Psychosis~~ ~~4. Euphoria~~ ~~5. Mood disorders: depression and anxiety if they rise to a level of a disorder~~ 6. Suicidal thoughts, ideation or gestures
Genitourinary 1. Priapism	~~**Genitourinary**~~ ~~1. Priapism~~