16.1.1 Protocol and Protocol Amendments

The latest global version of the protocol used during the study is provided in this section. Previous and country-specific versions of the protocol are available on request.

For Study ZX008-1501:

Protocol ZX008-1501 Amendment 3.0 dated 31-October-2016

For Study ZX008-1502:

Protocol ZX008-1502 Amendment 2.0 dated 31-October-2016

Clinical Study Protocol

Study Title:	A Multicenter, Randomized, Double-blind, Parallel Group, Placebo- controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome
Study Number:	ZX008-1501
Study Product:	Fenfluramine Hydrochloride Oral Solution; ZX008
IND Number:	125797
EudraCT Number:	2015-004167-37
Sponsor:	Zogenix International Limited A wholly owned subsidiary of Zogenix, Inc. 5858 Horton Street, Suite 455 Emeryville, CA 94608 USA
Sponsor's Medical Contact:	[redacted]
Date of Study Protocol:	31 October 2016 (Protocol Amendment 3.0) 18 January 2016 (Protocol Amendment 2) 18 December 2015 (Protocol Amendment 1) 02 November 2015 version 1.3 (Original Protocol)

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:	ZX008-1501
Study Title:	A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome
Sponsor's Responsible Officer:	Gail M. Farfel, PhD Director Zogenix International Limited A wholly owned subsidiary of Zogenix, Inc. 5858 Horton Street, Suite 455 Emeryville, CA 94608 USA

[redacted]

Signature

2 NOV 2016

Date (Day/Month/Year)

SIGNATURE OF COORDINATING INVESTIGATOR

Study Number: ZX008-1501

Study Title: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

Coordinating Investigator: Joseph Sullivan, MD

Director, Pediatric Epilepsy Center
University of California San Francisco
San Francisco, CA USA

[redacted]

Signature

03NOV2016

Date (Day/Month/Year)

SIGNATURE(S) OF THE PRINCIPAL INVESTIGATOR

Study Number: ZX008-1501

Study Title: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

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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 & Affiliation):

Signature **Date (Day/Month/Year)**

LIST OF ABBREVIATIONS

ABBREVATION	DEFINITION
AE	Adverse Event
AED	antiepileptic drug
AESI	Adverse Event of Special Interest
ANCOVA	analysis of covariance
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
BRIEF	Behavior Rating Inventory for Executive Function
C-SSRS	Columbia-Suicide Severity Rating Scale
CBD	cannabidiol
CFR	Code of Federal Regulations
C_{max}	Maximum observed concentration determined directly from the concentration-time profile
CYP	cytochrome P450
dL	Deciliter
DS	Dravet syndrome
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	electronic Case Report Form
EOS	End of study
EPAR	European Public Assessment Report
EQ-5D-5L	Standardized measure of health status
ET	Early Termination
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GH	Growth Hormone
GMP	Good Manufacturing Practices
HADS	Hospital Anxiety and Depression Scale
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDSMC	Independent Data and Safety Monitoring Committee
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor-1
IMP	Investigational Medicinal Product
IPCAB	International Pediatric Cardiology Advisory Board
IRB	Institutional Review Board
ABBREVATION	DEFINITION
IU	International Unit
IVR	Interactive Voice Response
IWR	Interactive Web Response (System)
KD	Ketogenic diet
kg	Kilogram
LH	Luteinizing Hormone
MCSF	Mean Convulsive Seizure Frequency

ABBREVATION	DEFINITION
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/kg/day	milligram per kilogram per day
min	Minutes
mITT	modified Intent-to-Treat
mL	Milliliter
PedsQL	Pediatric Quality of Life Inventory
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
SD	Standard Deviation
SMEI	Severe Myoclonic Epilepsy Of Infancy
SUDEP	Sudden Unexpected Death in Epilepsy
T+M	Titration plus Maintenance Periods
t1/2	terminal half-life
THC	tetrahydrocannabinol
Tmax	time to maximum concentration
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USA	United States of America
USP	United States Pharmacopeia
VNS	Vagal Nerve Stimulator/Stimulation
ZX008	Fenfluramine Hydrochloride Oral Solution

STUDY SYNOPSIS

Study Title: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome	
Study Number: ZX008-1501	
Study Product: Fenfluramine Hydrochloride Oral Solution, ZX008	
Type of Study: Efficacy, safety, and pharmacokinetics study	**Indication Studied:** Adjunctive therapy in Dravet syndrome
Phase of Development: Phase III	**Countries**: North America
Sponsor: Zogenix International Limited	
Coordinating Investigator: Joseph Sullivan, MD [redacted] University of California, San Francisco San Francisco, CA USA	
Estimated Duration of Individual Subject Participation: The duration of the participation in the study for an individual subject is expected to be up to 22 weeks, with a follow-up 3 to 6 months after the last dose of study medication for final safety monitoring.	
Objectives: The primary objective of the study is: • To demonstrate that ZX008 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment 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). The key secondary objectives of the study are: • To demonstrate that ZX008 0.2 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome based on change in the frequency of convulsive seizures between baseline and T+M. • To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) 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. See Statistical Methods (Section 10.5.1.3) for hierarchical testing procedure. Additional secondary efficacy objectives of the study are: • To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints: o The number of convulsive seizure-free days. o The proportion of subjects who achieve ≥75% reductions from baseline in convulsive seizure frequency. o The change from baseline in non-convulsive seizure frequency. o The change from baseline in convulsive + non-convulsive seizure frequency. o The incidence of rescue medication usage. o The incidence of hospitalization to treat seizures.	

- The incidence of status epilepticus.

- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints:
  - Clinical Global Impression – Improvement rating, as assessed by the principal investigator.
  - Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver.
  - The change from baseline in the Quality of Life in Childhood Epilepsy (QOLCE) score to measure quality of life.
  - The change from baseline in the Pediatric Quality of Life Inventory™ (PedsQL) score.
  - The change from baseline in PedsQL Family Impact module score.
  - The change from baseline in the quality of life (QoL) of the parent/caregiver using the EQ- 5D-5L scale.
  - The change from baseline in affective symptoms of the parent/caregiver using the Hospital Anxiety and Depression Scale (HADS).

The safety objective of the study is:

- To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day 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), and body weight. Cognitive Function will be assessed in subjects 5 years and older using the cognition domain score on the QOLCE. Cognitive function will be assessed using and age-appropriate versions of the BRIEF

The pharmacokinetics (PK) objective of the study is:

- To characterize the PK of ZX008 0.2 and 0.8 mg/kg/day at steady state in subjects ages 2-6 years and ≥6-18 years with Dravet syndrome.

The exploratory objectives of the study are:

- To compare the ZX008 0.2 and 0.8 mg/kg/day doses on primary, secondary, safety and PK endpoints.

Methodology:

This is a multicenter, double-blind, parallel-group, placebo-controlled, study to assess the efficacy, safety, and PK of ZX008 when used as adjunctive therapy in pediatric and young adult subjects with Dravet syndrome. Approximately 30 study sites in North America are planned to participate. 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 (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 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 over a 14-day Titration Period. Following titration, subjects will continue treatment at their randomly assigned dose over a 12-week Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is 14 weeks. At the end of the Maintenance Period (or early discontinuation), all subjects will undergo a 2-week taper or transition period (Post-Dosing Follow-Up) depending on whether they exit the study or are enrolled in the separate long-term open-label extension study. 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 study.

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 1.

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.

Number of Subjects:

Approximately 130 subjects will be screened to obtain 115 subjects who enter the Baseline Period. Of these 115 subjects, it is estimated that 105 subjects will be randomized into the Titration Period. Each clinical site will not randomize more than a maximum of 10 subjects without prior consent from the sponsor.

Inclusion Criteria: All 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 last 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 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, tonic-atonic, tonic-clonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.

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 has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
8. Subject has provided assent in accordance with Institutional Review Board (IRB) requirements, if capable.
9. Subject's parent/caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.

Exclusion Criteria: All subjects must meet none of the following exclusion criteria to 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 is at imminent risk of self-harm or harm to others, in the investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must be excluded if they report suicidal behavior in the past 6 months as measured by the C-SSRS at Screening or Baseline, which includes suicidal ideation with intent and plan (Item #5). If a subject reports suicidal ideation on Item 4 without specific plan, and the investigator feels that the subject is appropriate for the study considering the potential risks, the investigator must document appropriateness for inclusion, and discuss with the parent/caregiver to be alert to mood or behavioral changes, especially around times of dose adjustment.
6. Subject has a current or past history of glaucoma.
7. Subject has moderate or severe hepatic impairment. 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.
8. Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine- oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; or cyproheptadine (see Appendix 1). (Note: Short- term medication requirements will be handled on a per case basis by the Medical Monitor.)
9. Subject is currently receiving or has received stiripentol in the past 21 days prior to Screening.
10. Subject is currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy.
11. 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.

12. Subject has positive result on urine tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at the Screening Visit.
13. Subject has participated in another clinical trial within the past 30 days.
14. Subject is currently receiving an investigational product.
15. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
16. 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: Subjects must meet all of the inclusion criteria above plus the following criteria, to be randomized:

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 3 weeks.
4. Subject's parent/caregiver has been compliant with diary completion during the Baseline Period, in the opinion of the investigator (e.g., at least 90% compliant).

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. Subjects will be randomized to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 mg/day) or placebo. Study medication will be administered twice a day (BID) in equally divided doses with food.

Reference Product, Dose, and Mode of Administration:
Matching ZX008 placebo is supplied as an oral solution.

Duration of Treatment:
All subjects will receive ZX008 or matching placebo for up to approximately 16 weeks (Titration Period=2 weeks; Maintenance Period=12 weeks; Taper/Transition Period=2 weeks). After completion of the Maintenance Period, eligible subjects may enroll in the open-label extension study, after completion of the transition. Subjects who do not enroll in the open-label extension study will undergo a taper off of study medication (doses will be administered in a blinded fashion similar to the titration, i.e., doses will be decreased in 4-day increments). 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:
Efficacy:

- Number of seizures by type
- Convulsive seizure-free interval
- Clinical Global Impression – Improvement as assessed by parent/caregiver
- Clinical Global Impression – Improvement as assessed by principal investigator
- QOLCE to measure changes in quality of life of the subject
- PedsQL to measure changes in quality of life of the subject
- PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver

- QoL of parent/caregiver using the EQ-5D-5L scale
- Affective symptoms of parent/caregiver using the HADS scale
- Duration of prolonged seizures (seizure type that, during baseline, had duration >2 minutes)
- Number of episodes of status epilepticus
- Number of instances of rescue medication use and number of doses
- Number of inpatient hospital admissions due to seizures

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. The BRIEF will be administered to track cognitive function.

Pharmacokinetics:
Steady-state plasma fenfluramine PK parameters (maximum observed concentration determined directly from the concentration time profile [C_{max}], area under the concentration time curve from time zero to time=t [AUC_{0-t}], time to maximum concentration [T_{max}], and terminal half-life [$t_{1/2}$]) after administration of ZX008 derived using population PK methods.

Sample Size Determination:
The results of the only randomized, placebo-controlled studies in subjects with Dravet syndrome can be found in the European Public Assessment Report (EPAR) for stiripentol (EMA, 2007). The EPAR summarizes the results from two studies: STICLO France and STICLO Italy. In the stiripentol 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 0.8 mg/kg/day 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. Similar assumptions and calculations yield a requirement for an additional 35 subjects in the 0.2 mg/kg/day ZX008 group. Thus, the total sample size is planned to be 105 subjects (35 per arm).

Statistical Methods:
Study Populations:
Safety Population: All safety analyses will be performed on the Safety Population defined as all randomized subjects who receive at least one dose of study medication. Subjects will be analyzed according to the treatment actually received.

Modified Intent-to-Treat (mITT) Population: The mITT Population is defined as all randomized subjects who receive at least one dose of study medication and for whom at least 1 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 0.8 mg/kg/day to placebo as well as key secondary efficacy assessments will be performed on the mITT Population.

Per Protocol (PP) Population: The PP Population is defined as all randomized subjects who receive at least one dose of ZX008 or placebo, complete the Maintenance Period, and have no major protocol violations that would have a significant impact on clinical outcome.

Efficacy
Primary Efficacy Analysis: 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 (three levels) and age group (< 6 years, ≥6 years) as factors, and with Baseline MCSF as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day 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 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 echocardiogram, C-SSRS, Tanner Staging results, etc, will be summarized appropriately, by treatment. All safety summaries will be based on the Safety Population.

Pharmacokinetics

A population PK model will be fit to the fenfluramine concentration-time data collected during the Maintenance Period. This model will be informed by all relevant data available at the time of data collection (both adults and pediatrics). The population mean and interindividual variability estimates from the fit of the population PK model will be summarized. Derived plasma PK parameters (C_{max}, $AUC_{0\text{-}t}$, T_{max}, and $t_{1/2}$) will be summarized descriptively by treatment group and compared to historical data from adults. Summary statistics for plasma concentrations will be provided by PK sampling time.

Table 1: Schedule of Assessments

	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Post-Dosing	Cardiac Follow-up
				Titration Period			Maintenance Period							
Study Assessments	**Screening**		**Random-ization**											
Visit Number	**1**	**2 (Phone)**	**3**		**4, 5 (Phone)**	**6**	**7 (Phone)**	**8**	**9 (Phone)**	**10**	**11 (Phone)**	**12**	**13**	**14**
Study Day	**-42**	**-21**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**197-281**
Informed Consent (subject and parent)	X													
Inclusion/Exclusion Criteria	X		X											
Demographics	X													
Medical/Neurological History	X													
Epilepsy history	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[c]
Neurological Examination, complete	X											X		
Neurological Examination, abbreviated			X			X								
Vital signs	X		X			X		X		X		X		
Weight, Height, BMI	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	X[e]		X[e]			X[e]		X[e]		X[e]		X[e]		
Clinical laboratory evaluation (hematology/clinical chemistry/urinalysis,etc)	X		X			X		X		X		X		
Plasma sample for ZX008 pharmacokinetics								4X[f]						
Plasma sample for background AEDs			X[g]			X[g]		X[g]				X[g]		
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	R	C/R/D	R	C/R/D	R	C/R/D[h]	C/R	
Epilepsy genotype panel	X[l]													
Study Medication			D		R[i]	C/R/D	R	C/R/D	R	C/R/D	R	C/R/D[h]	C/R	
C-SSRS	X		X			X		X		X		X		

Table 1: Schedule of Assessments continued

Study Assessments	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Post-Dosing	Cardiac Follow-up
	Screening		Random-ization	Titration Period			Maintenance Period							
Visit Number	**1**	**2 (Phone)**	**3**		**4, 5 (Phone)**	**6**	**7 (Phone)**	**8**	**9 (Phone)**	**10**	**11 (Phone)**	**12**	**13**	**14**
Study Day	**-43 to -42 or -42 to -41**	**-21**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**197-281**
Clinical Global Impression - Improvement (assessed by parent/caregiver)						X		X		X		X		
Clinical Global Impression - Improvement (assessed by principal investigator)						X		X		X		X		
BRIEF			X					X				X		
QOLCE			X					X				X		
PedsQL			X					X				X		
EQ-5D-5L (QoL of parent/caregiver)			X									X		
HADS (Affect of parent/caregiver)			X					X				X		
Randomize subject			X											
First Day of Study Drug Administration				X[j]										
Daily Diary Completion	X													
Concomitant Medication	X													
Adverse events	X													
Adverse events of special interest	X													X[k]

AED=antiepileptic drug; BMI=body mass index; BRIEF=Behavior Rating Inventory of Executive Function; C=Collect; CBD=cannabidiol; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination; EQ-5D- 5L=standardized measure of health status; HADS=Hospital Anxiety and Depression Scale; PedsQL=Pediatric Quality of Life Inventory; QoL=quality of life; QOLCE=Quality of Life in Childhood Epilepsy; R=Review

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 an up to 2-week period.

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 study (see Section 6.4).

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 pharmacokinetic assessment will be conducted prior to the dose at Visit 8 and 1, 2, and 4-6 hours after dose administration.
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 Period for subjects entering the open-label extension study and for the Taper Period 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.

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 (DS).

DS, 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 (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. Dravet children 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 DS 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

DS 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 DS 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, and only in Europe, Canada, Japan, and Australia, as adjunctive therapy in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome), and must be co-administered with clobazam and valproate. Stiripentol has not been approved for use in the United States of America, but is available under compassionate use protocols at certain clinical sites.

[redacted] 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 treatment of DS; the efficacy and safety of this therapeutic approach have been published in a peer reviewed journal

(Ceulemans 2012; Ceulemans 2016) and reported to be very favorable. There are no treatments specifically approved for the treatment of DS in the United States of America (USA). Accordingly, there remains an unmet need for an approved treatment for children with DS.

1.1.2 Other Antiepileptic Medications

USA and European Union approved anti-epileptic drug products include valproate, topiramate, carbamazepine, oxcarbazepine, lamotrigine, benzodiazepines, phenobarbital, potassium bromide, ethosuximide, phenytoin, and vigabatrin. The treatment of DS 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 DS. In fact, some commonly used anti- epileptic drugs with a sodium channel mechanism of action, such as carbamazepine, oxcarbazepine, phenytoin, and lamotrigine, make DS worse.

A review of the treatment modalities used for DS has been published by Chiron and Dulac (Chiron and Dulac 2011). This review indicates that valproate 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 the benefit of these compounds is mild and there are no trials to validate the impression of any effect.

Given the cognitive consequences believed to be caused, at least in part, by frequent childhood seizure activity, there is a medical need for a new anticonvulsant treatment that can significantly reduce seizure activity in DS. There is the possibility that early, effective seizure control could be disease-modifying, leading to an improvement in longer-term outcomes with respect to motor impairment, behavioral issues, and cognitive function.

1.2 BACKGROUND INFORMATION ON STUDY PRODUCT

Zogenix is developing a new formulation of fenfluramine hydrochloride, ZX008, for the adjunctive treatment of DS. Fenfluramine is an amphetamine analogue that was first synthesized many years ago. It was approved in a large number of countries and widely prescribed as an appetite suppressant for the treatment of adult obesity. Brand names for fenfluramine formulations included Ponderax, Pondimin and others. Fenfluramine was also

used extensively in an off-label combination with phentermine ("Fen-Phen"). Fenfluramine is a racemic compound and the single enantiomer D-fenfluramine (dexfenfluramine) was also approved and marketed as Adifax, Redux, and others.

Fenfluramine was introduced in the USA in 1973. Products containing fenfluramine and D-fenfluramine were withdrawn from the USA market in 1997 after reports of heart valve disease and pulmonary hypertension (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 DS 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 of fenfluramine, norfenfluramine and their respective isomers has been studied in mice, rats, dogs and humans. The pharmacokinetics 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 pharmacokinetics and metabolism of fenfluramine after oral administration. In humans, fenfluramine is metabolized primarily to norfenfluramine. CYP1A2, CYP2B6, and CYP2D6 appear to be the predominant CYP 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 nordexfenflurmaine (7%-8%) from the body. Because fenfluramine and its active metabolite norfenfluramine have multiple pathways of elimination, interference with a single pathway is unlikely to cause a significant change in fenfluramine's clearance though the probability of an interaction increases if multiple elimination mechanisms are affected simultaneously.

While in vitro studies showed that both fenfluramine and norfenfluramine cause weak inhibition of CYP2D6 and fenfluramine causes weak induction of CYP3A4 and CYP2B6, further analysis based on the FDA's mechanistic static model shows that fenfluramine and its major metabolite norfenfluramine are unlikely to alter the pharmacokinetics of substrates of 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 equivalent to a human dose of 1.94 mg/kg/day based on

body surface area, and provides a safety factor of 2.4 for the highest dose of 0.8 mg/kg/day that will be administered clinically.

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

Based on several published reports of fenfluramine's successful treatment of refractory childhood epilepsy in the 1980s (Aicardi and Gaustaut 1985; Aicardi 1988) and its successful treatment of 11 refractory pediatric epilepsy patients in Belgium (Boel 1996), in 2002 Drs.

Ceulemans and Lagae were granted authorization to prescribe fenfluramine to their patients with refractory pediatric epilepsy conditions, including DS, under an approved protocol under a Belgium government program (Royal Decree). To date, these pediatric neurologists have DS patients (infants, children, young adults, and now also adults), being successfully treated with fenfluramine [redacted] The efficacy and safety of this therapeutic approach has been reported to be overwhelmingly favorable. In the most recent assessment of efficacy of these patients reported by the investigators in 2016, the average length of treatment was over 12 years, with one patient being successfully treated for 26 years (Ceulemans 2016). Of the 15 DS treated patients, 10 (67%) were reported as seizure-free, with the average time of seizure-freedom being 6 years (range 1-19 years). Twelve patients (87%) had a greater than 90% reduction in seizure frequency and 14 patients (93%) with greater than 70% reduction in seizure frequency.

In addition, numerous publications discuss the use of fenfluramine in over 500 children with neurobehavioral conditions for the treatment of mostly autism and ADHD, without any reports of any cardiovascular adverse events (ZX008 IB 2016).

Prior to being withdrawn from the market, fenfluramine was marketed at doses of 20 mg and 40 mg three times daily for the management of obesity in adults. The doses tested thus far in DS range from 0.12 to 0.9 mg/kg/day in subjects over 1 year of age to adults. Doses tested in pediatric studies evaluating autism and ADHD ranged from 0.65 mg/kg/day to 3.6 mg/kg/day, but a commonly used dose was 1.5 mg/kg/day. Occasionally, fixed doses of 30 to 80 mg were used. The PK exposure associated with the proposed doses in DS studies of 0.2 mg/kg/day and 0.8 mg/kg/day administered orally (in equally divided doses BID) is expected to be lower than that obtained at the doses used in the past for the treatment of obesity in adults and of neurobehavioral conditions in children and adolescents (ZX008 IB 2016). The doses used in this study are based on the data from the DS patients being successfully treated in Belgium discussed above.

There are no treatments specifically approved for the treatment of DS in the USA, and in fact, commonly used anticonvulsants with a sodium channel mode of action, such as phenytoin and

carbamazepine, worsen the condition. Accordingly, there remains a significant unmet need for an approved treatment for children and adults with DS.

1.6 RISK-BENEFIT ASSESSMENT

As described above, fenfluramine has been used successfully [redacted] in some DS patients to control seizures, without emergence of clinical valvulopathy or pulmonary hypertension. Fenfluramine was administered to over 500 children with neurobehavioral conditions, including autism and ADHD with good safety and tolerability, most often at a 1 mg/kg dose.

The pharmacologic and toxicological profile for the active pharmaceutical ingredient, fenfluramine, following oral administration is well established (see ZX008 IB 2016).

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

The approximate volume of blood (108.7 mL) planned for collection from each subject over the course of the entire study (Screening to End of Study, but not including repeat or additional tests ordered by the investigator) presents no undue risk to the subjects.

The ZX008 0.2 mg/kg/day and 0.8 mg/kg/day doses are believed to be therapeutic doses, which could provide sufficient anti-epileptic support for a sustained period of time during the study.

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

The primary objective of the study is:

- To demonstrate that ZX008 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment 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).

2.2 KEY SECONDARY OBJECTIVES

The key secondary objectives of the study are:

- To demonstrate that ZX008 0.2 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome based on change in the frequency of convulsive seizures between baseline and T+M.
- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) 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.

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

2.3 ADDITIONAL SECONDARY OBJECTIVES

Other secondary objectives of the study are:

- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) 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.
- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints:
  - Clinical Global Impression – Improvement rating, as assessed by the principal investigator.
  - Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver.
  - The change from baseline in the QOLCE score.
  - The change from baseline in the PedsQL score.
  - The change from baseline in the PedsQL Family Impact module score.
  - The change from baseline in the QoL of the parent/caregiver using the EQ-5D-5L scale.
  - The change from baseline in the affective symptoms of the parent/caregiver using the HADS.

2.4 SAFETY OBJECTIVE

The safety objective of the study is:

- To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day to placebo with regard to AEs, laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate [HR], temperature, and respiratory rate), ECGs, ECHOs, and body weight. Cognitive Function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the BRIEF.

2.5 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective of the study is:

- To characterize the PK of ZX008 0.2 and 0.8 mg/kg/day at steady state in subjects ages 2-6 years and >6-18 years with Dravet syndrome.

2.6 EXPLORATORY OBJECTIVE

The exploratory objective of the study is:

- To compare the ZX008 0.2 and 0.8 mg/kg/day doses on primary, secondary, safety and PK endpoints.

2.7 STUDY ENDPOINTS

2.7.1 Efficacy Endpoints

The efficacy endpoints of the study are:

- Number of seizures by type
- Convulsive seizure-free interval
- Clinical Global Impression – Improvement as assessed by parent/caregiver
- Clinical Global Impression – Improvement as assessed by principal investigator
- QOLCE to measure changes in quality of life of the subject
- PedsQL to measure changes in quality of life of the subject
- PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver
- QoL of the parent/caregiver using the EQ-5D-5L scale
- Affective symptoms of the parent/caregiver using the HADS scale
- Duration of prolonged seizures (seizure type that, during baseline, had duration
- >2 minutes)

- Number of episodes of status epilepticus
- Number of instances of rescue medication use and number of doses
- Number of inpatient hospital admissions due to seizures

2.7.2 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
- BRIEF to measure cognition.

2.7.3 Pharmacokinetic Endpoints

The PK endpoints of the study are:

- Steady-state plasma fenfluramine PK parameters (C_{max}, AUC_{0-t}, T_{max}, and $t_{1/2}$) after administration of ZX008 derived using population PK methods

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This is a multicenter, double-blind, parallel-group, placebo-controlled, study to assess the efficacy, safety, and PK of ZX008 when used as adjunctive therapy in pediatric and young adult subjects with Dravet syndrome. Approximately 30 study sites in North America are planned to participate. 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 (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 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 over a 14-day Titration Period. Following titration

subjects will continue treatment at their randomly assigned dose over a 12-week Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is 14 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 1.

At the end of the Maintenance Period (or early discontinuation), all subjects will undergo a 2-week taper or transition period (Post-Dosing Follow-Up) depending on whether they exit the study or are enrolled in the separate long-term open-label extension study.

A follow-up ECHO, ECG, and possibly physical examination 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 study.

3.2 NUMBER OF SUBJECTS

Approximately 130 subjects will be screened to obtain 115 subjects who enter the Baseline Period. Of these 115 subjects, it is estimated that 105 subjects will be randomized into the Titration Period. Each clinical site will not randomize more than a maximum of 10 subjects without prior consent from the sponsor.

3.3 STUDY DURATION

The duration of participation in the study for an individual subject is expected to be up to 22 weeks, plus follow-up safety visit 3 to 6 months after the last dose:

- Baseline Period – 6 weeks
- T+M Period - 14 weeks
- Post-Dosing Visit – 2 weeks 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 study.

3.4 NUMBER OF STUDY CENTERS

The study expects to use up to approximately 30 research centers in North America. Additional study centers within or outside of North America may be added if enrollment cannot be completed in a timely manner.

3.5 RATIONALE FOR STUDY DESIGN AND CHOICE OF TREATMENT GROUPS

It is recognized that performing clinical studies in young children or in subjects with reduced cognitive capacity presents particular practical and ethical issues. However, given the seriousness of DS, and the possible consequences of current inadequate treatments, the use of children with

DS in this study is considered justified. Stratifying the randomization 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 aged 6 -18 years. The study design has incorporated a titration period to enable subjects randomized to the high dose group adequate time to acclimate to this dose. 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.

Subjects will receive investigational medicinal product (IMP; 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. 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 will be able to receive ZX008 in an open-label extension study for up to 1 additional year of treatment.

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 6.2.9 and Section 6.3.

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)/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.

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

The IDMSC 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 pharmacokinetic data and any other data that may affect subject continuation.
- Make recommendations regarding the continuation, suspension, or termination of the study.

3.7.2 International Pediatric Cardiac Advisory Board (IPCAB)

The IPCAB is an advisory body to the sponsor that monitors cardiac safety of the ZX008 clinical trials and provides advice to the IDMSC. The IPCAB charter outlines the roles and responsibilities of the committee and guide its operations, and review of 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.). 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 adverse event, 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, member 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, as supplied by the sponsor.

4.1 INCLUSION CRITERIA

Subjects meeting all of the following inclusion criteria may 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 last 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 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, tonic-atonic, tonic-clonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.
6. All medications or interventions for epilepsy (including KD and VNS) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
7. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.

8. Subject has provided assent in accordance with Institutional Review Board (IRB) requirements, if capable.
9. Subject's parent/caregiver is willing and able to be compliant with diary completion, visit schedule 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 is at imminent risk of self-harm or harm to others, in the investigator's opinion, based on clinical interview and/or responses provided on the C-SSRS. Subjects must be excluded if they report suicidal behavior in the past 6 months as measured by the C-SSRS at Screening or Baseline, which includes suicidal ideation with intent and plan (Item #5). If a subject reports suicidal ideation on Item 4 without specific plan, and the investigator feels that the subject is appropriate for the study considering the potential risks, the investigator must document appropriateness for inclusion, and discuss with the parent/caregiver to be alert to mood or behavioral changes, especially around times of dose adjustment.
6. Subject has a current or past history of glaucoma.
7. Subjects with moderate or severe hepatic impairment may not be entered. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3xULN and/or elevated bilirubin <2xULN) may be entered into the study after review and approval by the Medical Monitor in conjunction with the sponsor, with consideration of potential cause, concomitant medications, and other risk factors.
8. Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; or cyproheptadine (see Appendix 1). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)
9. Subject is currently receiving or has received stiripentol in the past 21 days prior to Screening.
10. Subject is currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy.

11. 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.
12. Subject has positive result on urine THC Panel or whole blood CBD at the Screening Visit.
13. Subject has participated in another clinical trial within the past 30 days.
14. Subject is currently receiving an investigational product.
15. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
16. 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

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

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 (e.g., at least 90% compliant).

4.4 SUBJECTS OF REPRODUCTIVE POTENTIAL

Male subjects who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus 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:
    - 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 childbearing 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 childbearing 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 (i.e., condom for male partner):
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation and a barrier method (i.e., 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 volunteer is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery. Any subject reporting a pregnancy during the study will be withdrawn from the study and should complete the taper schedule.

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 (i.e., 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 (e.g., 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 IDMSC 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 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 (e.g., due to suspicion of fraud, multiple enrollments in clinical studies, lack of compliance).

The IDSMC may request that the study be terminated after review of the safety information at any time during the study. The IDMSC 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 (e.g., 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 6.2.9 and Section 6.3. 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

Enough subjects will be enrolled in the trial to ensure that approximately 105 subjects are randomized into the T+M Period. Randomized subjects will not be replaced.

4.8 ELIGIBILITY FOR EXTENSION STUDY

Subjects who complete the 12-week Maintenance Period of this study will be eligible to enroll in a planned, separate, open-label extension trial of ZX008 if they meet Inclusion/Exclusion criteria for that study regarding their suitability for continued participation in a trial of fenfluramine.

Subjects must complete the entire 12-week Maintenance Period in order to be offered enrollment into the separate, open-label extension trial of ZX008. Those subjects who do not complete 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 study 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 study 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 2).

Table 2: 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

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 also will be provided. Doses to be studied include 0.2 mg/kg/day and

0.8 mg/kg/day divided into two daily (BID) doses, up to a maximum of 30 mg/day. An intermediate dose of 0.4 mg/kg/day will be used for titration. The concentration of ZX008 oral solution received by subjects (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) will be randomized across the 3 available concentrations in order to ensure blinding.

If the parent/caregiver is unable to administer the full dose due to spillage (e.g., 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 Labeling and Packaging

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 Labeling and Packaging

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 (59-77°F) with excursions of 5-30°C (41-86°F) 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.

Assignment of ZX008 or placebo 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 drug accountability form provided by the sponsor before the start of the study. At the end of the study, the dated and signed (by the investigator or delegate, e.g., 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 Randomization

Upon completion of the Baseline Period, subjects who qualify for the study will be randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; 30mg/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 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 0.2 mg/kg/day, ZX008 0.8 mg/kg/day, 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.

5.5.2 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 (kg) at

Visit 3 (Study Day -1). At Visit 8 (Study Day 43), if the subject's weight (kg) has changed ±25% of the weight at Study Day-1, the IMP dose will be recalculated. Subjects should be dosed using the oral dosing syringe provided.

In order to maintain the blind across all dose groups (Section 5.6) and allow step titration to the high dose, the dose for each subject will be titrated starting with a dose of ZX008

0.2 mg/kg/day (or placebo equivalent) BID. After 4 days at this dose level (Study Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group will increase their dose to 0.4 mg/kg/day (maximum 30 mg/day) while doses in the other two groups will remain constant. On Study Day 9, the dose for the 0.8 mg/kg/day group will increase to the target dose or a maximum of 30 mg/day. The titration is expected to take a total of 14 days (Table 3). A new bottle of IMP will be started by the subject at each level of the titration step. See Section 5.6 for more information about the volume of ZX008 or placebo to be administered.

Table 3: Titration Algorithm

Randomized Group	Titration Step 1 Study Day 1-4	Titration Step 2 Study Days 5-8	Titration Step 3 Study Days 9-14
ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.8 mg/kg/day
Placebo	Placebo	Placebo	Placebo
Note: maximum daily dose of ZX008 is 30 mg			

5.5.3 Maintenance Period

After completion of the Titration Period, subjects will enter the Maintenance Period and continue to receive the randomized dose of ZX008 or placebo and be treated for an additional 12 weeks. Study medication will continue to be administered BID in the morning and in the evening, approximately 12 hours apart, 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.

5.5.4 Taper Period

Subjects who complete of the Maintenance Period and will not be continuing into the open-label extension study, and subjects who discontinue from the study early, will be tapered off of study medication. 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. IMP should be administered using the oral dosing syringe provided.

In order to maintain the blind across all dose groups, all subjects who do not continue into the

open-extension study will participate in a dose-tapering procedure over the course of 8 days. On the first day of the tapering period subjects in the ZX008 0.8 mg/kg/day group will decrease to a dose of ZX008 0.4 mg/kg/day BID (maximum 30 mg/day). After 4 days at this dose level (Study Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group will decrease their dose to 0.2 mg/kg/day. Subjects in the ZX008 0.2 mg/kg/day group will decrease their dose to placebo on the first day of tapering while doses in the placebo group will remain constant throughout the tapering procedure. On Study Day 9, all subjects will stop taking study medication. The taper is expected to take a total of 8 days (Table 4). A new bottle of IMP will be started by the subject at each level of the taper step.

Table 4: Taper Algorithm

Randomized Group	Taper Step 1 Day 1-4 after study completion or early termination	Taper Step 2 Days 5-8 after study completion or early termination
ZX008 0.2 mg/kg/day	Placebo	Placebo
ZX008 0.8 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
Placebo	Placebo	Placebo
Note: maximum daily dose of ZX008 is 30 mg.		

5.5.5 Transition Period

Subjects who complete the Maintenance Period and will be continuing into the open-label extension study will be transitioned from double-blind study medication to open-label ZX008 (Table 5). 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 should be administered using the oral dosing syringe provided.

All subjects entering the open-label extension study will be transitioned from their blinded daily dose (placebo, 0.2 mg/kg/day, 0.8 mg/kg/day, or 30 mg/day) to the 0.2 mg/kg dose during the 2-week interval between Visits 12 and 13, without breaking the blind. The IVR/IWR system will assign two bottles of IMP to the subject, one for each step in the transition. 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 5: Transition Algorithm

Dose Group in Double-Blind Study	Transition Step 1 Day 1-4 after Visit 12	Transition Step 2 Days 5-14 after Visit 12
ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day

Placebo	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
Note: maximum daily dose of ZX008 is 30 mg.		

Subjects who had been randomized to placebo increase their dose to 0.2 mg/kg/day beginning on Day 1 of the transition (the day following Visit 12). Subjects who had been randomized to 0.2 mg/kg/day will continue to receive that dose. Subjects who had been randomized to 0.8 mg/kg/day or were receiving the maximum dose of 30 mg/day decrease to a dose of ZX008 0.4 mg/kg/day, or a maximum of 30 mg/day. After 4 days at this dose level (Day 5), these subjects will decrease their dose to 0.2 mg/kg/day. Subjects will report to the clinic on Day 15 for enrollment into the open-label extension study.

5.6 BLINDING

At the end of the Baseline Period, subjects who qualify to enter the study will be randomized to receive ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day (maximum dose: 30 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 blinding scheme instituted for this study will ensure that the volume of study medication taken cannot be associated with the dose group, thus unblinding the study. This is achieved by random assignment of different concentrations of the ZX008 oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the IVR/IWR system. 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, and 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 and to the concentration of ZX008 oral solution. If an investigator feels the blind should be broken, he/she can do so when necessary for treatment decisions. However, the investigator should endeavor to discuss with the Medical Monitor or Sponsor's Medical Representative, if available. 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 the event. The subject will be discontinued from the clinical trial upon breaking of the blind and the decision whether the subject can enter the separate open-label extension study will rest with the Sponsor if the subject exited Study 1501 prior to completion.

5.7 PRIOR AND CONCOMITANT MEDICATION

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 (e.g., 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 medication 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 decrease in a concomitant AED 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 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 CRF.

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 CRF.

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 medication 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 Medication and Food

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 following concomitant medications are prohibited during the clinical trial:

- AEDs: Phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, retigabine/ezogabine
- Stiripentol (STP): Subjects must be off STP for a minimum of 21 days prior to the Screening visit.
- 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.
- Drugs that interact with central serotonin, including but not limited to: imipramine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, vortioxetine
- Drugs that increase cardiovascular risk including: atomoxetine and those with noradrenergic reuptake properties (NRIs, SNRIs)
- 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.

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

Study procedures will be conducted according to the Schedule of Assessments in Table 1.
Time windows for all assessments are detailed in Table 6.

Table 6: Time Windows for Assessments

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Clinic; Study Day -43 to -42 or -42 to -41):	Not applicable
Visit 2 (Phone; Study Day -21)	± 3 days
Visit 3 (Clinic; Study Day -1; Randomization)	+ 4 days[a]
Visits 4, 5 (Phone: Study Days 4, 8)	± 3 days
Visit 6 (Clinic; Study Day 15)	± 4 days
Visit 7 (Phone: Study Day 29)	± 4 days
Visit 8 (Clinic; Study Day 43)	± 4 days

Visit 9 (Phone: Study Day 57)	± 4 days
Visit 10 (Clinic; Study Day 71)	± 4 days
Visit 11 (Phone: Study Day 85)	± 4 days
Visit 12 (Clinic: Study Day 99)	± 4 days
Visit 13 (Clinic; Study Day 113; 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

a In cases where the screening period is extended beyond 42 days, the immediate 42 days before the Randomization visit will be used to calculate the baseline seizure frequency

6.1 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.

6.1.1 Screening, Clinic Visit 1 (Study Day -42)

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 (e.g., 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 PedsQL Family Impact, HADS, and 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

- Record prior medications
- Complete physical examination, including height, weight, and calculation of BMI
- Complete neurological examination
- 12-lead electrocardiogram
- Doppler ECHO (this may be obtained any time between Study Day -42 and Study Day -21)
- Vital signs
- 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
- 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 DS 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 re-screened 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.

6.1.2 Phone Visit 2 (Study Day -21)

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

- AEs
- AESI

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

6.1.3 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 pharmacokinetic 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
- 12-lead ECG
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, and hematology, and urinalysis)
- Collect plasma sample for AED pharmacokinetic 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)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6)
- PedsQL Family Impact module (Appendix 6)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- Affective symptoms of parent/caregiver using the HADS scale (Appendix 8)
- Record AEs
- Record AESI
- When eligibility for the Titration Period is confirmed, randomize (blinded) subject to treatment assignment (ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day, 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 TITRATION AND MAINTENANCE PERIODS

6.2.1 Titration Period Study Day 1

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

6.2.2 Phone Visits 4 and 5 (Titration Period Study Days 4 and 8)

Site personnel will contact the subject via telephone on Titration Period Study Days 4 and 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.

6.2.3 Clinic Visit 6 (Titration Period Study Day 15)

Subjects will report to the clinic in the morning on Titration Period Study Day 15. 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
- Obtain vital signs
- 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 AED pharmacokinetic 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)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (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

6.2.4 Phone Visit 7 (Maintenance Period Study Day 29)

Site personnel will contact the subject via telephone on Maintenance Period Study Day 29 and record the following:

- AEs
- AESI
- Concomitant medications

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

6.2.5 Clinic Visit 8 (Maintenance Period Study Day 43)

- Subjects will report to the clinic in the morning on Maintenance Period Study Day 43. 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 Study Day-1, the IMP dose will be recalculated)

- Obtain vital signs
- 12-lead electrocardiogram
- Doppler ECHO (this must be obtained any time between Study Day 40 and Study 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 ZX008 pharmacokinetic evaluation at the following timepoints: within 1 hour prior to the morning dose of study medication, and 1, 2 and 4-6 hours after the morning dose of study medication
- Collect plasma sample for AED pharmacokinetic 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)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6)
- PedsQL Family Impact module (Appendix 6)
- Affective symptoms of parent/caregiver using the HADS scale (Appendix 8)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (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

6.2.6 Phone Visit 9 (Maintenance Period Study Day 57)

Site personnel will contact the subject via telephone on Maintenance Period Study Day 57 and record the following:

- AEs
- AESI
- Concomitant medications

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

6.2.7 Clinic Visit 10 (Maintenance Period Study Day 71)

Subjects will report to the clinic on Maintenance Period Study Day 71. 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
- Obtain vital signs
- 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)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (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

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

6.2.8 Phone Visit 11 (Maintenance Period Study Day 85)

Site personnel will contact the subject via telephone on Maintenance Period Study Day 85 and record the following:

- AEs
- AESI
- Concomitant Medications

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

6.2.9 Clinic Visit 12 (Maintenance Period Study Day 99): End of Study/Early Termination

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 study if they have completed 12 weeks of treatment in the Maintenance Period. Other circumstances for participation in the extension study 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 study 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 study 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
- Obtain vital signs
- 12-lead electrocardiogram
- Doppler ECHO (must be performed any time between Study Day 90 and Study
- Day 113; if subject terminates 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 (see Table 7).
- 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 AED pharmacokinetic 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)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (assessed by investigator)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6)
- PedsQL Family Impact module (Appendix 6)

- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- Affective symptoms of parent/caregiver using the HADS scale (Appendix 8)
- Record AEs
- Record AESIs
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

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

6.3 POST-DOSE VISIT (CLINIC VISIT 13; STUDY DAY 113)

For subjects entering the open-label extension study, the subject will visit the clinic on Day 113. 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
- AESIs
- Concomitant medications
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

If the subject does not enter the open-label extension study (or discontinues from the study early), the subject will visit the clinic on Study Day 113 (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
- AESIs
- Concomitant medications
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

6.4 CARDIAC FOLLOW-UP VISIT (CLINIC VISIT 14; STUDY DAY 197-281)

If the subject completes the study but does not enter the open-label extension study 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 in Table 7. 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 than 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 7: 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 and 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 and 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

[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.

6.5 ESTIMATED BLOOD VOLUME COLLECTION

The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately 99.7 mL, as outlined in Table 8.

Table 8: Estimated Blood Volume Collection*

Assessment	Baseline Period (study day)			Titration + Maintenance Period (study day)			
	Screening (Day -42 to -41)	Randomization Day -1	Day 15	Day 43	Day 71	Day 99	Total
Clinical Chemistry	4mL	4mL	4mL	4mL	4mL	4mL	24mL
LH, FSH, Estradiol, Testosterone, Prolactin		4mL		4mL	4mL	4mL	16mL
Genotyping	5 mL						5 mL
Hematology	2mL	2mL	2mL	2mL	2mL	2mL	12mL
IGF-1, GH		2.5mL		2.5mL	2.5mL	2.5mL	10 mL
Coagulation		2.7mL					2.7mL
Cannabidiol	2mL	2mL	2mL	2mL	2mL	2mL	12mL
ZX008 PK plasma				4 x 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	13mL	19.2mL	10mL	26.5mL	14.5mL	16.5mL	**99.7 mL**

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 43/Visit 8 the pharmacokinetic 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 9:

Table 9: 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

7. EFFICACY, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

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

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

7.1 EFFICACY ASSESSMENTS

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)

B: Focal With or Without Retained Awareness

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)

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 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 (e.g. 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

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.

The CGI scale measures the change in the subject's clinical status from a specific point in time, i.e., 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 document in the source file prior to rating.

7.1.3 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. 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).

The cognitive domain of the QOLCE consists of the following subscales: attention/concentration, memory, languages, and "other cognition". Each of these subscales have shown good internal reliability and consistency (Cronbach's alpha > 0.80) in the population aged 4 and above. The cognitive domain of the QOLCE will be used to assess cognition during study participation in the population aged 5 and older as of the subject's age at baseline.

7.1.4 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL (Appendix 6) is a pediatric modular measure of health-related QoL completed by

the parent/caregiver on behalf of the subject. It consists of 4 core scales that measure physical, emotional, social, and school functioning. The PedsQL will be conducted according to the schedule in Table 1.

7.1.5 Parent/Caregiver Quality of Life

The impact on the quality of life of the parent/caregiver responsible for a patient with DS will be assessed according to the schedule in Table 1 using 3 scales: the EQ-5D-5L, the HADS, 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 HADS (Appendix 8) is a tool commonly used to determine the levels of anxiety and depression that a person is experiencing. It is a 14-item scale that generates ordinal data. Seven of the items relate to anxiety and 7 relate to depression.

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 DS has impacted their quality of life using the scales described above.

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.

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. 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. 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.

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 8:

- 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), carbon dioxide (CO_2), chloride (Cl), creatinine, creatine kinase, gamma-glutamyl transferase (GGT), globulin, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), thyroid function (T3, T4, and thyroid stimulating hormone [TSH]), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid.
- 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
- Coagulation: Prothrombin time (PT)/International normalized ratio (INR), activated partial thromboplastin time (PTT)
- Whole blood cannabidiol
- 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 (i.e., classified as an abnormal, clinically significant value) at any visit after screening will be documented in the eCRF as an AE (see Section 9).

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. 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.

7.2.7 Electrocardiograms

Twelve-lead ECGs will be conducted during study as outlined in Table 1 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 the investigator's overall interpretation will be recorded.

7.2.8 Doppler Echocardiography

Doppler echocardiography will be conducted at a facility with experience for the subject's age during study as outlined in Table 1. 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 10 (Adverse Events of Special Interest). A manual of proper ECHO technique for sites is provided in a separate document.

7.2.9 Tanner Staging

Tanner Staging (Appendix 5) will be assessed for subjects >7 years old during the study as outlined in Table 1. 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'.

7.2.10 Columbia-Suicide Severity Rating Scale

C-SSRS (Appendix 2) will be assessed during study as outlined in Table 1. 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.

7.2.11 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 9.

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.

7.2.12 Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF is a standardized, validated rating scale to measure executive function in children ages 2-18within the home and school environments; it will be assessed according to the schedule in Table 1. 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), and Plan/Organize/Organization of Materials (anticipate future events; set goals; develop steps; grasp main ideas), and Monitor (check work; assess own performance).

7.3 PHARMACOKINETIC ASSESSMENTS

Blood samples for PK assessments of fenfluramine and its metabolite (norfenfluramine) will be obtained from all subjects via an indwelling cannula or by venipuncture.

Blood samples for PK assessment (2 mL) will be obtained at the following time points:

- Maintenance Period Study Day 43: 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.

7.4 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 (i.e., 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, e.g., 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 (e.g., cosmetic surgery).
    - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (e.g., 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 (e.g., hemolysis) and flagged as such by the laboratory in the laboratory report.
3. Abnormal parameters that are obviously biologically implausible (e.g., values that

are incompatible with life).

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

8.1.2 Serious Adverse Events

A serious adverse event (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 (e.g., 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 status epilepticus (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 AESIs for the ZX008 program (Table 10).

Table 10: Adverse Events of Special Interest

CV/Respiratory
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.
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 a systolic pressure ≥140 mmHg after repeated measures during one visit. Blood pressure should be repeated at appropriate times within the visit.
5. Jugular venous distention- visible bulging of the external jugular veins on either side of the neck
6. New onset heart murmur
7. Pulmonary rales – an abnormal respiratory sound heard during auscultation of the lungs, which is also described as a crackle.
8. Tachycardia – a persistent HR >30% above the screening value and unrelated to exercise, exertion or anxiety. Heart rate should be repeated at appropriate times within the visit.
9. 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
10. Signs on ECHO indicative of potential valvulopathy • 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
11. Signs on ECHO indicative of pulmonary hypertension a. Tricuspid Regurgitation Jet velocity > 2.8 msec 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 caval vein (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/sec vi. Tricuspid Anular Plane Systolic Excursion below 18 mm or below Z-score – 2

continued

Table 10: Adverse Events of Special Interest (continued)

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 – serum blood glucose more than 20% below the glucose level on Study Day -1 value or more than 10% below LLN (reference range 60 – 140 mg/dL)
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

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, magnetic resonance imaging (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 11).

Table 11: 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.
CDISC SDTM 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), 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 (e.g., natural history of the underlying disease, concomitant medication) 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 (e.g., headache, facial flushing, pallor)
- Plausibility supported by the temporal relationship (e.g., 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:

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

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 study, 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 a 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 iHC 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.

Adverse events occurring in the period between the time the subject gave written informed consent and the first exposure to IMP that meet one or more of the seriousness criteria for AEs must be reported to the sponsor and the Medical Monitor in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs 15 days after the last dose of study drug or the last visit, whichever is later that is considered to be causally related to IMP must be **reported immediately (i.e., within 24 hours of the investigator becoming aware of the event) to the sponsor and 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 (e.g., 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 (e.g., 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. In the event of a SAE a blood sample for ZX008 and AED PK should be collected as soon as feasible.

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.

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, triscuspid) 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 11 describes the severity of ECHO findings with the level of increasing oversight if the subject is to remain in the study.

Table 12: Clinical Measures Enacted Upon Increasing Severity of ECHO Findings

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

Level 1: Continue per protocol

Level 2:

1. If there is a desire to continue study medication:
    a. The investigator will evaluate the efficacy to date based on study diaries and consult with the parent/guardian, and determine whether study treatment was associated with significant, meaningful benefit in number, severity and/or duration of seizures and/or on the impact on daily functioning.
    b. The investigator will consider whether the subject has had reasonable trials (dose and duration) of other available anticonvulsants (e.g. valproic acid, clobazam, or topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.
2. If the investigator feels consideration of continued treatment is warranted considering benefit and potential risk, and the parent/guardian feels strongly that the child be maintained on the study medication when understanding the risks, the parent/guardian must sign a new consent which describes the additional risk and the child should provide assent if appropriate.
    a. If both of these conditions are not met, the subject is discontinued from treatment.
3. 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 risk and proposed monitoring plan if applicable, for submission to the IDSMC.
5. IDMSC 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 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 (e.g., valproic acid, clobazam, topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.
2. If the investigator feels consideration of continued treatment is warranted considering benefit and potential risks, and the parent/guardian feels strongly that the child be maintained on the study medication when understanding the risks, the parent/guardian must sign a new consent, which describes the additional risks and the child should provide assent if possible.
   a. If both of these conditions are not met, the subject is discontinued from treatment.
3. 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 subjects 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 FDA 21 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 (e.g., 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

The results of the only randomized, placebo-controlled studies in subjects with Dravet syndrome can be found in the European Public Assessment Report (EPAR) for stiripentol (EMA, 2007). The EPAR summarizes the results from two studies: STICLO France and STICLO Italy. In the stiripentol groups, the 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 0.8 mg/kg/day 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. Similar assumptions and calculations yield a requirement for an additional 35 subjects in the 0.2 mg/kg/day ZX008 group. Thus, the total sample size is planned to be 105 subjects (35 per arm).

10.2 ANALYSIS POPULATIONS

10.2.1 Safety (SAF) Population

All safety analyses will be performed on the 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 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 ZDX008 0.8 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 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 will be randomly assigned to one of three treatment groups: ZX008 0.8 mg/kg/day, ZX008 0.2 mg/kg/day, or placebo.

10.4 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 first 14 days of treatment while subjects are titrated to their randomized dose. It begins on the first day of treatment (Study Day 1) and extends through Study Day 15 regardless of the exact day on which a subject reaches his or her assigned dose. 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. It begins on Study Day 16 and extends through Study Day 99.

Titration +Maintenance (T+M) Period

The T+M period combines the Titration and Maintenance periods, beginning on Study Day 1 and extending through Study Day 99. 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 to a final visit 2 weeks later; i.e., from Study Day 99 through Study Day 113. Only subjects who do not roll over enrollment into the open-label extension will participate in the Follow-up Period.

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, standard deviations, 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.

Efficacy and PK data will be summarized by treatment (ZX008, placebo) age cohort (<6 years and ≥6 years of age), as well as for the total subjects in the population.

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

10.5.1 Efficacy Analyses

10.5.1.1 Primary Efficacy Analysis

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 (three levels) and age group (< 6 years, ≥6 years) as factors, and with baseline frequency as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day 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 such as the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day 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.

An additional analysis will be performed to assess the sensitivity of the primary analysis to changes in dose or type of concomitant AED medications that may occur during the course of the trial, which are protocol violations. Specifically, the primary analysis will be repeated with a factor added to indicate whether a subject had a change in prescribed dose or type of concomitant AED medication during the T+M period. Further exploratory analyses may be conducted if changes in concomitant AED medication appear to have a significant impact on the primary outcome.

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

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 0.8 mg/kg/day 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 0.8 mg/kg/day and placebo groups will be compared using a log-rank test.

The MCSF in the ZX008 0.2 mg/kg/day group will be compared to the placebo group using the same methods employed for the primary analysis. Analyses of other key secondary endpoints involving the ZX008 0.2 mg/kg/day group will employ similar methods as those used to compare ZX008 0.8 mg/kg/day to placebo. Whenever feasible, secondary analyses involving either ZX008 0.8 mg/kg/day or ZX008 0.2 mg/kg/day 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

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 beginning with comparisons of ZX008 0.8 mg/kg/day to placebo 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 evaluation of key secondary endpoints continues by comparing the ZX008 0.2 mg/kg/day group to placebo in the following order:

- 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.

10.5.2 Safety Analyses

Summaries of safety data will be presented by treatment – ZX008 0.8 mg/kg/day, ZX008 0.2 mg/kg/day 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 serious AEs (SAEs). Selected summaries will be repeated broken out by age group, i.e., for ages <6 years and ≥6 years.

Hematology and chemistry laboratory results 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. 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 echocardiogram, C-SSRS, Tanner Staging results, etc, will be summarized appropriately, by treatment. All safety summaries will be based on the SAF Population.

10.5.3 Pharmacokinetic Analyses

All data will be evaluated using population PK analysis methods and the methods will be described in detail in a separate PK analysis plan. In brief, the plan is to use published data to construct a population PK model for fenfluramine in adults. Given the age range of subjects to be enrolled in this study, it will be possible to use the known ontogeny of drug disposition in children to predict fenfluramine PK in subjects with Dravet syndrome from the population PK model. The robustness of the empirical model will then be confirmed by applying the model to PK data collected from this study. In this way, the effect of body size, age, and any other relevant factors can be quantified to assure that an adequate understanding of fenfluramine PK is obtained.

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: the population mean and interindividual variability estimates from the fit of the population PK model; summary statistics of the plasma concentrations by PK sampling time and of the individual, derived plasma PK parameters (Cmax, AUC0-t, Tmax, and t1/2) by

treatment group. The clinical study report will also contain a comparison of the PK of fenfluramine in the children enrolled in this study to historical data from adults.

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 (e.g., 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/or 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 (i.e., 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.

This study will be conducted under Investigational New Drug (IND) Application and documented in accordance with the applicable regulatory guidelines and requirements.

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 (e.g., the European Data Protection Directive [95/46/EC] and the USA Health Insurance Portability and Accountability Act [HIPAA]), 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 (i.e., 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 (e.g., 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

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
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 SEVERITY 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

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

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

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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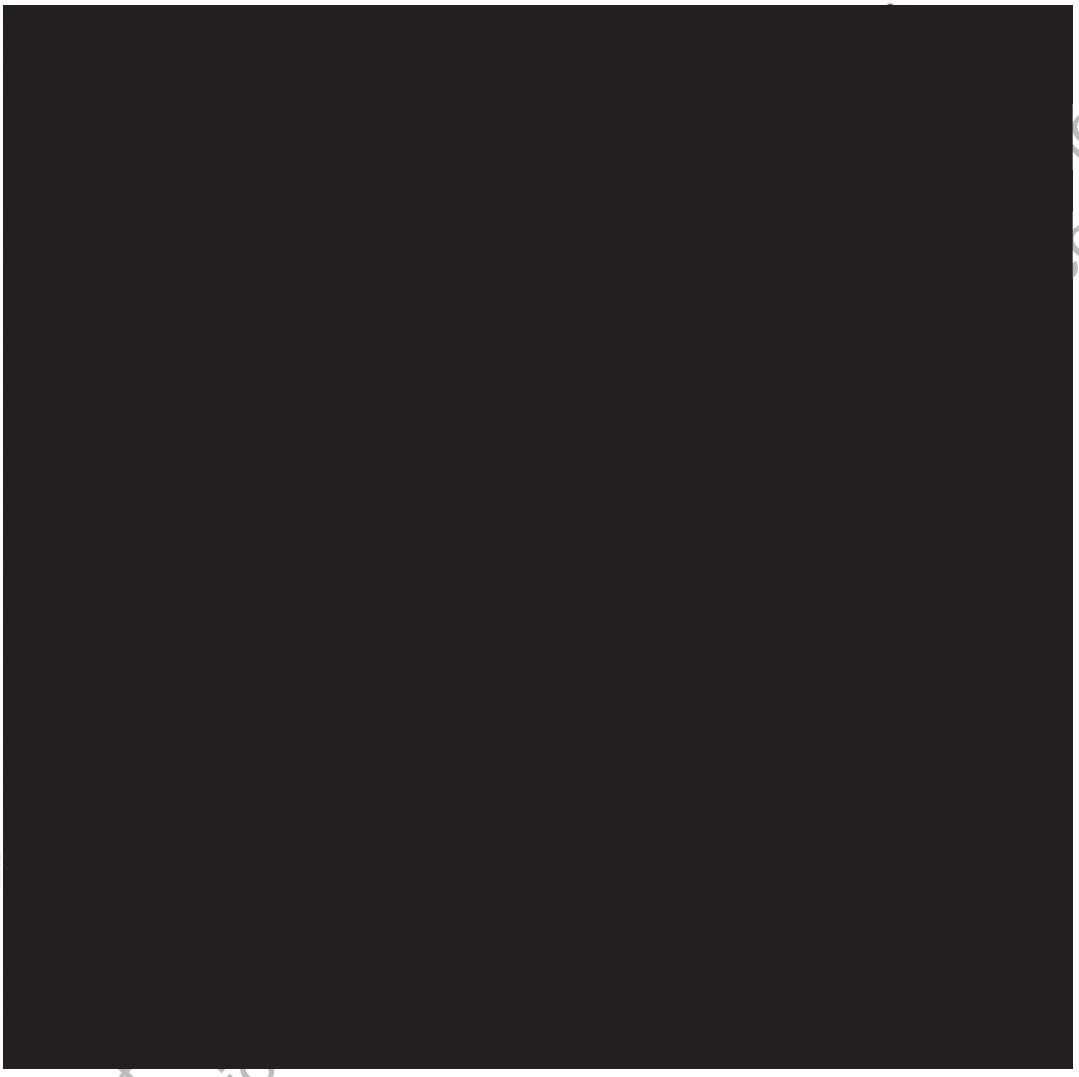
[redacted]



[redacted]

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.

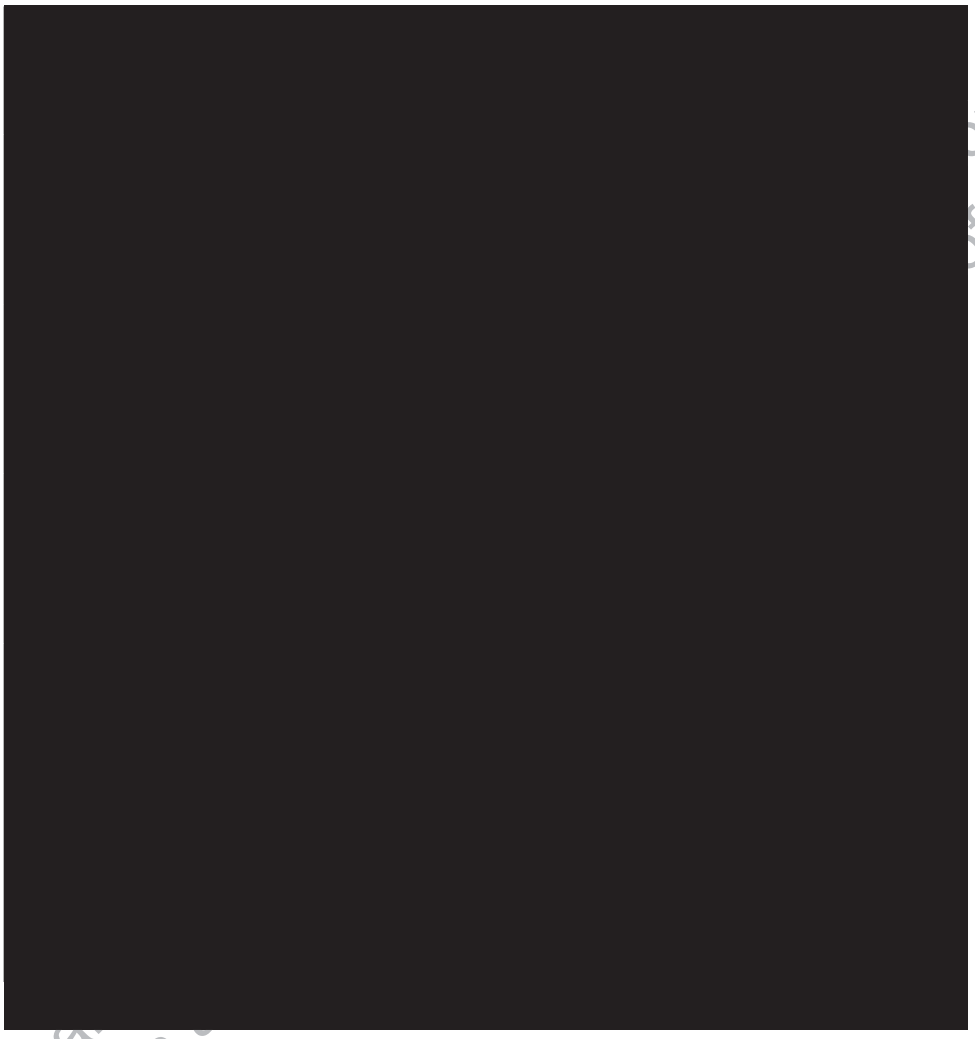
5. There are no right or wrong answers. If you are unsure how to answer a question, please give the best answer you can and make a comment in the margin.

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.

[redacted]

[redacted]



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 areolae.

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

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APPENDIX 6 – PEDSQL (INCLUDING FAMILY IMPACT MODULE)

APPENDIX 8 – HOSPITAL ANXIETY AND DEPRESSION SCALE

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 – PROTOCOL AMENDMENT 1

Summary of Changes

Clarifications and changes were made to the protocol and include the following:

- Sponsor name change
- Added new section of transition for subjects who will enter the open-label extension study
- Removed the following clinical laboratory tests at Visits 1 and 6: LH, FSH, estradiol, testosterone, GH, prolactin, and IGF-1
- Clarified the maximum dose of ZX008 is 30 mg/day
- Clarified the collection duration of prior and concomitant AEDs
- Clarified data to be collected with the use of rescue medication
- Moved the BRIEF-P description from the efficacy section to the safety section
- Added new section of collection of data for AEs requiring hospitalization

Additional clarifications and changes were made based on feedback received from the United States Food and Drug Administration, and include the following:

- Clarified randomization inclusion criteria, post-treatment cardiac follow-up, and AESI with regard to valve regurgitation seen on ECHO.
- Clarified that the central cardiac reader will provide consultation to the IDSMC when a subject may be removed from the study due to development of signs or symptoms indicative of valvulopathy, regurgitation, or pulmonary hypertension
- Clarified expedited reporting of cardiac events other than SAEs
- Added section on grading of and follow-up for ECHO findings

The rationale for each change/clarification also is provided below.

List of Specific Changes

Additions are marked in **bold** and deletions are marked in ~~strikethrough~~. Minor editorial changes, such as the correction of typing or formatting errors, updating headers and footers, and tables of contents, etc, are not listed.

Rationale: There has been a name change for the sponsor's subsidiary.	
Original Text	**Amendment Text**

Title page, Signature of Sponsor page, Synopsis, Table 2, and document headers Brabant Pharma Limited	Title page, Signature of Sponsor page, Synopsis, Table 2, and document headers ~~Brabant Pharma Limited~~ **Zogenix International Limited**
Rationale: A transition period for those subjects entering the open-label extension study has been added in order to preserve the study blind and allow all subjects to enter the follow-on study receiving	

open-label study medication.	
Original Text	**Amendment Text**
Synopsis Methodology: After completion of the Maintenance Period, eligible subjects will be offered enrollment in a separate open-label extension trial.	Synopsis Methodology: **At the end of the Maintenance Period (or early discontinuation), all subjects will undergo a 2-week taper or transition period (Post-Dosing Follow-Up) depending on whether they exit the study or are enrolled in the separate long-term open-label extension study.**
Duration of Treatment: All subjects will receive ZX008 or matching placebo for up to approximately 14 weeks (Titration Period=2 weeks; Maintenance Period=12 weeks). After completion of the Maintenance Period, eligible subjects may enroll in the open-label extension study.	Duration of Treatment: All subjects will receive ZX008 or matching placebo for up to approximately ~~14~~ **16** weeks (Titration Period=2 weeks; Maintenance Period=12 weeks**; Taper/Transition=2 weeks**). After completion of the Maintenance Period, eligible subjects may enroll in the open-label extension study**, after completion of the transition**.
Table 1. Schedule of Assessments, Footnotes c: Only for subjects who do not roll over into the open-label extension study. k: 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 study (see Section 6.4). l: Only adverse events related to cardiac safety will be collected at this visit.	*Table 1. Schedule of Assessments, Footnotes* *(appropriate adjustments were made within the table regarding these footnotes)* c: ~~Only for subjects who do not roll over into the open-label extension study.~~ **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 study (see Section 6.4).** k: ~~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 study (see Section 6.4).~~ **Only adverse events related to cardiac safety will be collected at this visit.** ~~l: Only adverse events related to cardiac safety will be collected at this visit.~~
Section 3.1 After completion of the Maintenance Period, eligible subjects will be offered enrollment in a separate open-label extension trial.	Section 3.1 ~~After completion of the Maintenance Period, eligible subjects will be offered enrollment in a separate open-label extension trial.~~ **At the end of the Maintenance Period (or early discontinuation), all subjects will undergo a 2-week taper or transition period (Post-Dosing Follow-**

None	**Up) depending on whether they exit the study or are enrolled in the separate long-term open-label extension study.** **5.5.5 Transition Period** **Subjects who complete the Maintenance Period and will be continuing into the open-label extension study will be transitioned from double-blind study medication to open-label ZX008 (Table 5). 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.** **All subjects entering the open-label extension study will be transitioned from their blinded daily dose (placebo, 0.2 mg/kg/day, 0.8 mg/kg/day, or 30 mg/day) to the 0.2 mg/kg dose during the 2-week interval between Visits 12 and 13, without breaking the blind. The IVR/IWR system will assign two bottles of IMP to the subject, one for each step in the transition. 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 5. Transition Algorithm** **Dose Group in Double-Blind Study** / **Transition Step 1 Day 1-4 after Visit 12** / **Transition Step 2 Days 5-14 after Visit 12** **ZX008 0.2 mg/kg/day** / **ZX008 0.2 mg/kg/day** / **ZX008 0.2 mg/kg/day** **ZX008 0.8 mg/kg/day** / **ZX008 0.4 mg/kg/day** / **ZX008 0.2 mg/kg/day** **Placebo** / **ZX008 0.2 mg/kg/day** / **ZX008 0.2 mg/kg/day** **Note: maximum daily dose of ZX008 is 30 mg.** **Subjects who had been randomized to placebo increase their dose to 0.2 mg/kg/day beginning on Day 1 of the transition (the day following Visit 12.) Subjects who had been randomized to 0.2 mg/kg/day will continue to receive that dose. Subjects who had been randomized to 0.8 mg/kg/day or were receiving the maximum dose**

	of 30 mg/day decrease to a dose of ZX008 0.4 mg/kg/day, or a max of 30 mg/day. After 4 days at this dose level (Day 5), these subjects will decrease their dose to 0.2 mg/kg/day. Subjects will report to the clinic on Day 15 for enrollment into the open-label extension study.
Section 6.2.7 None	Section 6.2.7 **At Clinic Visit 10, compliant subjects who have tolerated IMP should be presented with the ICF for the open-label extension study. Informed consent for the open-label extension study must be signed at Visit 12 or earlier in order to enter the open-label extension study.**
Section 6.2.9 □ Dispense study medication for taper subjects not enrolling in the open-label extension study	Section 6.2.9 □ Dispense study medication ~~for taper subjects not enrolling in the open-label extension study~~
None	**Informed consent for the open-label extension study must be signed at Visit 12 (if not signed earlier) in order to enter the open-label extension study.**
Section 6.3 None	Section 6.3 **For subjects entering the open-label extension study, the subject will visit the clinic on Day 113. 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** □ **AESIs** □ **Concomitant medications** □ **Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver**
Rationale: To remove the following clinical laboratory tests at Visits 1 and 6: LH, FSH, estradiol, testosterone, GH, prolactin, and IGF-1.	
Original Text	**Amendment Text**
Section 1.6 The approximate volume of blood (108.7 mL) planned for collection from each subject over the course of the entire study (Screening to End of	Section 1.6 The approximate volume of blood (~~115.7~~ **108.7** mL) planned for collection from each subject over the course of the entire study (Screening to End of Study, but not

Study, but not including repeat or additional tests ordered by the investigator) presents no undue risk to the subjects. Section 6.5 The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately 115.7 mL.	including repeat or additional tests ordered by the investigator) presents no undue risk to the subjects. Section 6.5 The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately ~~115.7~~ **108.7** mL.

Original Text

Table 8. Estimated Blood Volume Collection

Assessment	Baseline Period (study day)		Titration + Maintenance Period (study day)				
	Screening (Day -42 to -41)	Randomization Day -1	Day 15	Day 43	Day 71	Day 99	Total
Clinical chemistry	7.5 mL	7.5 mL	7.5 mL	7.5 mL	7.5 mL	7.5 mL	45 mL
LH, FSH, estradiol, testosterone, GH, prolactin	Included in Chemistry	Included in Chemistry	Included in Chemistry	Included in Chemistry	Included in Chemistry	Included in Chemistry	
Hematology	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	12 mL
Genotyping	5 mL	--	--	--	--	--	5 mL
IGF-1	3.5 mL	3.5 mL	3.5 mL	3.5 mL	3.5mL	3.5 mL	21 mL
Coagulation	--	2.7 mL	--	--	--	--	2.7 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 × 0.5 mL	--	--	2 mL
Approximate total blood volume per subject	20.0 mL	19.7 mL	17.0 mL	27.0 mL	15.0 mL	17.0 mL	115.7 mL

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

Amendment Text

Table 8. Estimated Blood Volume Collection

Assessment	Baseline Period (study day)		Titration + Maintenance Period (study day)				
	Screening (Day -42 to -41)	Randomization Day -1	Day 15	Day 43	Day 71	Day 99	Total
Clinical chemistry	7.5 mL	7.5 mL	7.5 mL	7.5 mL	7.5 mL	7.5 mL	45 mL
LH, FSH, estradiol, testosterone, GH, prolactin	~~Included in Chemistry~~ --	Included in Chemistry	~~Included in Chemistry~~ --	Included in Chemistry	Included in Chemistry	Included in Chemistry	
Hematology	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	12 mL
Genotyping	5 mL	--	--	--	--	--	5 mL
IGF-1	~~3.5 mL~~ --	3.5 mL	~~3.5 mL~~ --	3.5 mL	3.5mL	3.5 mL	~~21~~ **14** mL
Coagulation	--	2.7 mL	--	--	--	--	2.7 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 × 0.5 mL	--	--	2 mL
Approximate total blood volume per subject	~~20.0~~ **16.5** mL	19.7 mL	~~17.0~~ **13.5** mL	27.0 mL	15.0 mL	17.0 mL	~~115.7~~ **108.7 mL**

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

Rationale: To clarify the maximum dose of ZX008 is 30 mg/day.	
Original Text	**Amendment Text**
Section 5.5.2 After 4 days at this dose level (Study Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group will increase their dose to 0.4 mg/kg/day while doses in the other two groups will remain constant. On Study Day 9, the dose for the 0.8 mg/kg/day group will increase to the target dose.	Section 5.5.2 After 4 days at this dose level (Study Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group will increase their dose to 0.4 mg/kg/day **(maximum 30 mg/day)** while doses in the other two groups will remain constant. On Study Day 9, the dose for the 0.8 mg/kg/day group will increase to the target dose **or a maximum of 30 mg/day.**
Table 3 None	Table 3 **Note: maximum daily dose of ZX008 is 30 mg.**
Section 5.5.4 On the first day of the tapering period subjects in the ZX008 0.8 mg/kg/day group will decrease to a dose of ZX008 0.4 mg/kg/day BID.	Section 5.5.4 On the first day of the tapering period subjects in the ZX008 0.8 mg/kg/day group will decrease to a dose of ZX008 0.4 mg/kg/day BID (**maximum 30 mg/day)**.
Table 4 None	Table 4 **Note: maximum daily dose of ZX008 is 30 mg.**
Rationale: To clarify the collection duration of prior and concomitant AEDs.	
Original Text	**Amendment Text**
Section 5.7 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 (e.g., antiepileptic drugs [AEDs], antibiotics) taken within 30 days prior to the Screening visit should also be captured.	Section 5.7 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 (e.g., ~~antiepileptic drugs [AEDs]~~, 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**.
Rationale: To clarify data to be collected with the use of rescue medication.	
Original Text	**Amendment Text**
Section 5.7.3 Use of rescue medication is permitted during the study and should be recorded on the eCRF (day, time, medication[s], dose[s]) and in the diary (day, time). Repeated administrations within the same episode should be recorded separately.	Section 5.7.3 Use of rescue medication is permitted during the study and should be recorded on the eCRF (day, ~~time,~~ medication[s], dose[s]) and in the diary (day, time**frame associated with seizure episodes**). Repeated administrations within the same episode should be recorded separately.

Rationale: To move the BRIEF-P description from the efficacy section to the safety section	
Original Text	**Amendment Text**
7.1.4 Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P)	~~7.1.4~~ **7.2.12** Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P)
Rationale: To add new section of collection of data for AEs requiring hospitalization.	
Original Text	**Amendment Text**
None	**Section 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, magnetic resonance imaging (MRI), x-ray, computed tomography CT) scan, surgery, and lumbar puncture/spinal tap.**
Rationale: To clarify randomization inclusion criteria, post-treatment cardiac follow-up, and AESI with regard to valve regurgitation seen on ECHO.	
Original Text	**Amendment Text**
Synopsis, Section 4.3, Section 6.4, Section 8.1.3 Synopsis and Section 4.3 Randomization Inclusion Criteria: 2. Subject does not have a cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination, including but not limited to any mitral, aortic, tricuspid or pulmonary valve regurgitation or signs of pulmonary hypertension, and is approved for entry by the cardiac central reader. Section 6.4, Table 6, footnote b Positive sign or symptom includes any sign of valve thickening or regurgitation (mitral, aortic, pulmonary, tricuspid), or sign or symptom indicative of potential pulmonary hypertension as adjudicated by the IPCAB. Section 8.1.3, Table 8 10. Signs on ECHO indicative of potential	Synopsis, Section 4.3, Section 6.4, Section 8.1.3 Synopsis and Section 4.3 Randomization Inclusion Criteria**:** 2. Subject does not have a cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination, including but not limited to ~~any~~ **trace** mitral, **or** aortic~~, tricuspid or pulmonary~~ valve regurgitation or signs of pulmonary hypertension, and is approved for entry by the ~~cardiac~~ central cardiac reader. Section 6.4, Table 7 footnote b Positive sign or symptom includes any ~~sign~~ **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. Section 8.1.3, Table 9 10. Signs on ECHO indicative of potential valvulopathy

valvulopathy □ ≥ mild valve regurgitation (aortic, mitral, tricuspid, or pulmonary) □ Mean Mitral valve gradient ≥ 4 mmHg □ Mean Aortic valve gradient ≥ 15 mmHg □ Mean Tricuspid valve gradient > 4 mmHg □ Mean Pulmonary valve gradient > 21 mmHg	□ **valve regurgitation (aortic or mitral)** □ ≥ mild valve regurgitation (~~aortic, mitral,~~ tricuspid, or pulmonary) □ Mean Mitral valve gradient ≥ 4 mmHg □ Mean Aortic valve gradient ≥ 15 mmHg □ Mean Tricuspid valve gradient ~~>~~ ≥ 4 mmHg □ Mean Pulmonary valve gradient ~~>~~ ≥ 21 mmHg
Rationale: To clarify that the central cardiac reader will provide consultation to the IDSMC when a subject may be removed from the study due to development of signs or symptoms indicative of valvulopathy, regurgitation, or pulmonary hypertension.	
Original Text	**Amendment Text**
Section 4.5 Subjects may 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 and the investigator believe the benefit of continued participation does not outweigh the risk.	Section 4.5 Subjects may 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.
Rationale: To clarify expedited reporting of cardiac events other than SAEs.	
Original Text	**Amendment Text**
Section 8.8 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.* 4. Hypersensitivity reactions 5. Pulmonary hypertension 6. Cardiac symptoms requiring intervention, or valvulopathy	Section 8.8 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**

Rationale: To add a new section on grading of, and follow-up for, ECHO findings.

Original Text	Amendment Text
None	**Section 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, triscuspid) 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 11 describes the severity of ECHO findings with the level of increasing oversight if the subject is to remain in the study.** **Table 11. Clinical Measures Enacted Upon Increasing Severity of ECHO Findings** **Level 1: Continue per protocol** **Level 2:** **1. If there is a desire to continue study medication:** **a. The investigator will evaluate the efficacy to date based on study diaries and consult with the parent/guardian, and determine whether study treatment was associated with significant, meaningful benefit in number, severity and/or duration of seizures and/or on the impact on daily functioning.** **b. The investigator will consider whether the subject has had reasonable trials (dose and duration) of other available anticonvulsants (e.g. valproic acid, clobazam, or topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.**

	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

	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 IDMSC.** **5. IDMSC 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 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 risk of cardiopulmonary**

	complications, considering the subject's age and overall health. **c. Subject has had reasonable trials (dose and duration) of other available anticonvulsants (e.g., valproic acid, clobazam, topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.** **2. If the investigator feels consideration of continued treatment is warranted considering the benefit and potential risk, and the parent/guardian feels strongly that the child be maintained on the study medication when understanding the risks, the parent/guardian must sign a new consent, which describes the additional risk and the child should provide assent if 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 risk and proposed monitoring plan if applicable for submission to the IDMSC.** **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**

APPENDIX 11 – PROTOCOL AMENDMENT 2

Summary of Changes

Clarifications and changes were made to the protocol and include the following:

- Replaced CHU9D with PedsQL
- Updated statistical analysis section to be consistent with the separate statistical analysis plan
- Clarified inclusion criterion #7 regarding the requirement for a whole blood sample for a broad epilepsy-related gene panel

A change was made based on feedback received from the United States Food and Drug Administration, and include the following:

- Added the assessment of cognition for subjects ≥5 years of age, so that all study participants are now being assessed for cognition using the BRIEF. The description of the BRIEF was moved from the efficacy section to the safety section.

Clarifications and changes were made based on feedback received from the European Voluntary Harmonization Procedure Clinical Trials Group, and include the following:

- Updated contraception requirements for the study
- Clarified when subjects must be discontinued from the study
- Clarified that the investigator may discontinue a subject from the study in the case of a medical emergency
- Added statistical information regarding sensitivity analyses for concomitant AED medication changes during the study

The rationale for each change/clarification also is provided below.

List of Specific Changes

Additions are marked in **bold** and deletions are marked in ~~strikethrough~~. Minor editorial changes, such as the correction of typing or formatting errors, updating headers and footers, tables of contents, and list of references, etc, are not listed.

Rationale: To replace the CHU9D with the PedsQL for the assessment of quality of life.	
Original Text	**Amendment Text**

Synopsis, Section 2.3 Additional secondary efficacy objectives of the study are: □ To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints:	Synopsis, Section 2.3 Additional secondary efficacy objectives of the study are: □ To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints:

o The change from baseline in the Child Health Utility 9D Scale (CHU9D) score.	o The change from baseline in the ~~Child Health Utility 9D Scale (CHU9D)~~ **Pediatric Quality of Life Inventory™ (PedsQL)** score.
Synopsis (Criteria for Evaluation/Efficacy), Section 2.7.1 □ CHU9D to measure changes in quality of life of the subject	Synopsis (Criteria for Evaluation/Efficacy), Section 2.7.1 □ ~~CHU9D~~ **PedsQL** to measure changes in quality of life of the subject
Table 1 was updated and is not presented here.	Table 1 was updated and is not presented here.
Sections 6.1.3, 6.2.5, and 6.2.9 The following procedures will be performed: □ CHU9D (Appendix 6)	Sections 6.1.3, 6.2.5, and 6.2.9 The following procedures will be performed: □ ~~CHU9D~~ **Peds QL** (Appendix 6)
Section 7.1.4 Child Health Utility 9D Scale The CHU9D (Appendix 6) is a pediatric generic preference based measure of health-related QoL completed by the parent/caregiver on behalf of the subject. It consists of a descriptive system and a set of preference weights, giving utility values for each health state described by the descriptive system, allowing the calculation of quality adjusted life years for use in cost utility analysis. The CHU9D will be conducted according to the schedule in Table 1.	Section 7.1.4 ~~Child Health Utility 9D Scale~~ **Pediatric Quality of Life Inventory** The **PedsQL** ~~CHU9D~~ (Appendix 6) is a pediatric ~~generic preference based~~ **modular** measure of health-related QoL completed by the parent/caregiver on behalf of the subject. It consists of ~~a descriptive system and a set of preference weights, giving utility values for each health state described by the descriptive system, allowing the calculation of quality adjusted life years for use in cost utility~~ analysis **4 core scales that measure physical, emotional, social, and school functioning**. The **PedsQL** ~~CHU9D~~ will be conducted according to the schedule in Table 1.
Section 7.1.5 The impact on the quality of life of the parent/caregiver responsible for a patient with DS will be assessed according to the schedule in Table 1 using 2 scales: the EQ-5D-5L and the HADS. 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.	Section 7.1.5 The impact on the quality of life of the parent/caregiver responsible for a patient with DS will be assessed according to the schedule in Table 1 using ~~2~~ 3 scales: the EQ-5D-5L**,** ~~and~~ the HADS**, 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 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.**
Appendix 6 was updated and is not presented here.	Appendix 6 was updated and is not presented here.

Rationale: To update the statistical sections of the protocol to be consistent with the separate statistical analysis plan.

Original Text	**Amendment Text**
Synopsis, Section 3.1, Section 5.5.1 *Synopsis-Methodology* Randomization will be stratified by age group (< 6 years, ≥6 to 18 years) to ensure balance across treatment arms, and at least 40% of subjects will be in each age group.	Synopsis, Section 3.1, Section 5.5.1 *Synopsis-Methodology* Randomization will be stratified by age group (< 6 years, ≥6 ~~to 18~~ years) to ensure balance across treatment arms, and at least 40% of subjects will be in each age group.
Synopsis *Synopsis-Statistical Methods/Efficacy* Primary Efficacy Analysis: 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 (three levels) and age group (< 6 years, ≥6 to 18 years) as factors, and with Baseline MCSF as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day group to the placebo group using a two-sided test at the alpha=0.05 level of significance. Since the ANCOVA used in the primary analysis relies on assumptions of normality, the primary endpoint also will be analyzed using a nonparametric method that does not require as stringent assumptions. Specifically, the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the van Elteren test will be used to assess the primary objective.	Synopsis *Synopsis-Statistical Methods/Efficacy* Primary Efficacy Analysis: 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 (three levels) and age group (< 6 years, ≥6 ~~to 18~~ years) as factors, and with Baseline MCSF as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day 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.** ~~Since the ANCOVA used in the primary analysis relies on assumptions of normality, the primary endpoint also will be analyzed using a nonparametric method that does not require as stringent assumptions. Specifically, the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the van Elteren test will be used to assess the primary objective.~~
Section 10.5.1.1 The primary efficacy endpoint is the change in the	Section 10.5.1.1 The primary efficacy endpoint is the change in the mean

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 (three levels) and age group (< 6 years, ≥6 to 18 years) as factors, and with baseline frequency as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day 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. Specifically, the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the van Elteren 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. <u>Section 10.5.1.2</u> The longest interval between convulsive seizures will be calculated for each subject over the entire T+M period. Subjects whose longest interval extends to the end of treatment or end of study will be considered right-censored. The ZX008 0.8 mg/kg/day and	placebo groups will be compared using a log-rank

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 (three levels) and age group (< 6 years, ≥6 ~~to 18~~ years) as factors, and with baseline frequency as a covariate.
The primary analysis will compare the ZX008 0.8 mg/kg/day 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. ~~Specifically, **A nonparametric test such as** the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the ~~van Elteren~~ **nonparametric** test will be used to assess the primary objective.

An additional analysis will be performed to assess the sensitivity of the primary analysis to changes in dose or type of concomitant AED medications that may occur during the course of the trial, which are protocol violations. Specifically, the primary analysis will be repeated with a factor added to indicate whether a subject had a change in prescribed dose or type of concomitant AED medication during the T+M period. Further exploratory analyses may be conducted if changes in concomitant AED medication appear to have a significant impact on the primary outcome.

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.

Section 10.5.1.2
The longest interval between convulsive seizures will be calculated for each subject over the entire T+M period. ~~Subjects whose longest interval extends to the end of treatment or end of study will be considered right- censored.~~ The ZX008 0.8 mg/kg/day and placebo groups will be compared using a log-rank test. ~~The median~~

test. The median length of the longest seizure-free interval will be presented for each treatment group. Section 10.5.1.3 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. If any test fails to achieve significance at the α=0.05 level, then no test lower in the hierarchy can achieve statistical significance. Section 10.5.2 Selected summaries will be repeated broken out by age group, i.e., for ages <6 years and ≥6 to 18	~~length of the longest seizure-free interval will be presented for each treatment group.~~ Section 10.5.1.3 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. ~~If any test fails to achieve significance at the α=0.05 level, then no test lower in the hierarchy can achieve statistical significance.~~ Section 10.5.2 Selected summaries will be repeated broken out by age group, i.e., for ages <6 years and ≥6 ~~to 18~~ years.
Rationale: To clarify inclusion criterion #7 regarding the requirement for a whole blood sample for a broad epilepsy-related gene panel.	
Original Text	**Amendment Text**
Synopsis, Section 4.1 Subject agrees to provide whole blood sample for a Dravet syndrome genetic testing panel, if genetic screening results from an acceptable commercial laboratory or medical center are not available for SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, GABRD, GABRG2, and PCDH19.	Synopsis, Section 4.1 Subject agrees to provide whole blood sample for a **broad epilepsy-related gene testing panel** ~~Dravet syndrome genetic testing panel, if genetic screening results from an acceptable commercial laboratory or medical center are not available for SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, GABRD, GABRG2, and PCDH19~~.
Rationale: To add the assessment of cognition for subjects ≥5 years of age, so that all study participants are now being assessed for cognition using the BRIEF, and to move the description of the BRIEF from the efficacy section to the safety section.	
Original Text	**Amendment Text**
Synopsis, Section 2.4 The safety objective of the study is: o To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day 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), and body weight. Cognitive Function will be assessed in subjects 5 years and older using the cognition domain score on the QOLCE. Cognitive function in subjects <5 years at baseline will be assessed using the Brief Rating Inventory of Executive Function-Preschool version (BRIEF-P).	Synopsis, Section 2.4 The safety objective of the study is: o To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day 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), and body weight. ~~Cognitive Function will be assessed in subjects 5 years and older using the cognition domain score on the QOLCE.~~ Cognitive function ~~in subjects <5 years at baseline~~ will be assessed using **age-appropriate versions of** the Brief Rating Inventory of Executive Function ~~Preschool version~~ (BRIEF-~~P~~).

Synopsis (Criteria for Evaluation/Safety) • The cognition domain of the QOLCE will also be used to track cognitive function relative to baseline in children 5 years and older. The BRIEF-P will be administered to children younger than 5 years to track cognitive function. Table 1 was updated and is not presented here. Section 2.7.2 The safety endpoints of the study are: • Behavior Rating Inventory of Executive Function, Preschool Version (BRIEF-P) to measure cognition in subjects aged 2 to < 5 years at baseline • Cognition subscale of QOLCE will be used to assess cognitive function for children aged 5 years and older at baseline Sections 6.1.3, 6.2.5, and 6.2.9 The following procedures will be performed: • BRIEF-P for subjects < 5 years (Appendix 3) Section 7.1.12 The BRIEF-P is a standardized, validated rating scale to measure executive function in preschool aged children within the home and school environments that will be assessed according to the schedule in Table 1. The BRIEF-P measures multiple aspects of executive functioning; scales include Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. Appendix 3 was updated and is not presented here.	Synopsis (Criteria for Evaluation/Safety), Section 2.7.2 • ~~The cognition domain of the QOLCE will also be used to track cognitive function relative to baseline in children 5 years and older.~~ The BRIEF~~-P~~ will be administered to ~~children younger than 5 years to~~ track cognitive function. Table 1 was updated and is not presented here. Section 2.7.2 The safety endpoints of the study are: • ~~Behavior Rating Inventory of Executive Function, Preschool Version (~~ BRIEF~~-P)~~ to measure cognition ~~in subjects aged 2 to < 5 years at baseline~~ • ~~Cognition subscale of QOLCE will be used to assess cognitive function for children aged 5 years and older at baseline~~ Sections 6.1.3, 6.2.5, and 6.2.9 The following procedures will be performed: • BRIEF~~-P for subjects < 5 years~~ (Appendix 3) Section 7.2.12 The BRIEF~~-P~~ is a standardized, validated rating scale to measure executive function in ~~preschool aged~~ children **ages 2-18 years** within the home and school environments; ~~that~~ **it** will be assessed according to the schedule in Table 1. The BRIEF~~-P~~ 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).** Appendix 3 was updated and is not presented here.
Rationale: To update contraception requirements for the study.	
Original Text	**Amendment Text**
Section 4.4 Subjects who are sexually active must use, with their partner, 2 approved methods of highly effective contraception from the time of informed consent until	Section 4.4 ~~Subjects who are sexually active must use, with their partner, 2 approved methods of highly effective contraception from the time of informed consent until~~

90 days after the last dose of study medication.	~~90 days after the last dose of study medication.~~
Two or more of the following methods are acceptable and must include at least 1 barrier method: - Surgical sterilization (i.e., bilateral tubal ligation/salpingectomy, hysterectomy for female subjects or partners; vasectomy for male subjects or partners) - Placement of an intrauterine device or intrauterine system - Hormonal contraception (implantable, patch, oral, injectable) - Barrier methods (for male subjects, this must be a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps]; for female subjects, either their partner's use of a condom or the subject's use of an occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository)	~~Two or more of the following methods are acceptable and must include at least 1 barrier method:~~ - ~~Surgical sterilization (i.e., bilateral tubal ligation/salpingectomy, hysterectomy for female subjects or partners; vasectomy for male subjects or partners)~~ - ~~Placement of an intrauterine device or intrauterine system~~ - ~~Hormonal contraception (implantable, patch, oral, injectable)~~ - ~~Barrier methods (for male subjects, this must be a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps]; for female subjects, either their partner's use of a condom or the subject's use of an occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository)~~
Male subjects who have been sterilized or have partners of non-childbearing potential (including homosexual men) are required to use one barrier method of contraception (condom). This is to prevent unintended exposure of the partner to the study drug via seminal fluid.	~~Male subjects who have been sterilized or have partners of non-childbearing potential (including homosexual men) are required to use one barrier method of contraception (condom). This is to prevent unintended exposure of the partner to the study drug via seminal fluid.~~
Male subjects who have pregnant partners are required to use one barrier method of contraception (condom).	~~Male subjects who have pregnant partners are required to use one barrier method of contraception (condom).~~
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, must comply with the contraceptive requirements detailed above.	~~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, must comply with the contraceptive requirements detailed above.~~
Female subjects of non-childbearing potential, i.e., women who are post-menopausal (defined as spontaneous amenorrhea for at least 1 year without another cause or spontaneous amenorrhea for at least 6 months confirmed by a follicle stimulating hormone [FSH] result of ≥40 IU/mL), or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, as determined by subject medical history), are not required to use any contraception during this study.	~~Female subjects of non-childbearing potential, i.e., women who are post-menopausal (defined as spontaneous amenorrhea for at least 1 year without another cause or spontaneous amenorrhea for at least 6 months confirmed by a follicle stimulating hormone [FSH] result of ≥40 IU/mL), or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, as determined by subject medical history), are not required to use any contraception during this study.~~ **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 effective contraception from the time of informed consent until 90 days after study discharge. **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 30 days following the last follow up visit.** **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)** **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.**
Rationale: To clarify when subjects must be discontinued from the study.	
Original Text	**Amendment Text**
Section 4.5 Subjects may be discontinued from the study for the following reasons, if deemed appropriate by the sponsor or investigator: *(list of reasons is unchanged)*.	Section 4.5 Subjects ~~may~~ **must** be discontinued from the study for the following reasons, if deemed appropriate by the sponsor or investigator: *(list of reasons is unchanged)*.
Rationale: To clarify that the investigator may discontinue a subject from the study in the case of a medical emergency.	
Original Text	**Amendment Text**
Section 5.6 The blinding scheme instituted for this study will ensure that the volume of study medication taken cannot be associated with the dose group, thus unblinding the study. This is achieved by random assignment of different concentrations of the ZX008 oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the IVR/IWR system. 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 and to the concentration of ZX008 oral solution. The Medical Monitor will have the ability to unblind subjects in the case of an emergency.	Section 5.6 The blinding scheme instituted for this study will ensure that the volume of study medication taken cannot be associated with the dose group, thus unblinding the study. This is achieved by random assignment of different concentrations of the ZX008 oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the IVR/IWR system. 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 and to the concentration of ZX008 oral solution. ~~The Medical Monitor will have the ability to unblind subjects in the case of an emergency.~~ **If an investigator feels the blind should be broken, he/she can do so when necessary for treatment decisions. However, the investigator should endeavor to discuss with the Medical Monitor or Sponsor's Medical Representative, if available. 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 the event. The subject will be discontinued from the clinical trial**

	upon breaking of the blind and the decision whether the subject can enter the separate open-label extension study will rest with the Sponsor if the subject exited Study 1502 prior to completion.

APPENDIX 12 – PROTOCOL AMENDMENT 3

Summary of Changes

Clarifications and changes were made to the protocol and include the following:

- Removed atonic seizures and added tonic-atonic from the types of convulsive seizures in Inclusion Criterion #5.
- Removal of Inclusion Criterion #7 to clarify that participation in the epilepsy-related genetic testing is not required for participation.
- Updated the preclinical data information and, based on this information, revised the list of prohibited concomitant medications.
- Clarified that the number of convulsive seizures during the 6-week baseline period is ≥ 6.
- Added PedsQL Family Impact module to the efficacy measures.
- Clarify study days of Screening during the Baseline Period and the timing of assessments in that period.
- Collection of blood sample for epilepsy genotype panel is mandatory but not required at screening.
- Added the list of countries in which Diacomit® (stiripentol) is approved.
- Added supporting references to existing citations of data.
- Clarified the safety objective.
- Specify that the number of study centers is approximate.
- Clarified the duration of use of contraception after the last dose of study drug.
- Removal of social media policy from the reason or removing a subject from therapy or assessment.

The rationale for each change/clarification also is provided below.

List of Specific Changes

Additions are marked in **bold** and deletions are marked in ~~strikethrough~~. Minor editorial changes, such as the correction of typing or formatting errors, updating headers and footers, tables of contents, and list of references, etc, are not listed.

Rationale: To clarify the types of seizures that satisfy the requirement for the 12 weeks before screening.	
Original Text	**Amendment Text**
Inclusion Criterion, Synopsis and Section 4.1 Subject must have had ≥4 convulsive seizures (tonic-clonic, tonic, atonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.	Inclusion Criterion, Synopsis and Section 4.1 Subject must have had ≥4 convulsive seizures (tonic-clonic, tonic, **tonic-atonic**, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.
Rationale: Remove the requirement for participation in epilepsy-related gene testing from the inclusion	

criteria.	
Original Text	**Amendment Text**
Inclusion Criterion 7, Synopsis and Section 4.1 Subject agrees to provide whole blood sample for a broad epilepsy-related gene testing panel.	Inclusion Criterion 7, Synopsis and Section 4.1 ~~Subject agrees to provide whole blood sample for a broad epilepsy-related gene testing panel.~~
Rationale: Revised the list of prohibited concomitant medications.	
Original Text	**Amendment Text**
Exclusion Criterion 8, Synopsis and Section 4.2 Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; cyproheptadine, and/or cytochrome P450 (CYP) 2D6/3A4/2B6 inhibitors/substrates (see Appendix 1). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)	Exclusion Criterion 8, Synopsis and Section 4.2 Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; **or** cyproheptadine, ~~and/or cytochrome P450 (CYP) 2D6/3A4/2B6 inhibitors/substrates~~ (see Appendix 1). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)
Rationale: Clarified that the number of convulsive seizures during the 6-week baseline period is ≥ 6.	
Original Text	**Amendment Text**
Randomization Inclusion Criterion 3, Synopsis and Section 4.3 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. Section 6.1.3 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.	Randomization Inclusion Criterion 3, Synopsis and Section 4.3 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. Section 6.1.3 This period is intended to ensure that subjects meet the study entry criteria and confirm they have experienced ≥6 ~~>6~~ convulsive seizures during the 6-week Baseline Period, with at least 2 seizures in each 3-week half of the Baseline Period.
Rationale: Added PedsQL Family Impact module to the efficacy measures.	
Original Text	**Amendment Text**
Synopsis, Criteria for Evaluation: Efficacy Not applicable Section 2.3, Additional Secondary Objectives Not applicable Section 2.7.1, Efficacy Endpoints Not applicable Section 6.1.3, 6.2.9 Not applicable	Synopsis, Criteria for Evaluation: Efficacy **PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver** Section 2.3, Additional Secondary Objectives **The change from baseline in the PedsQL Family Impact module score.** Section 2.7.1, Efficacy Endpoints **PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver** Section 6.1.3, 6.2.9 **PedsQL Family Impact module (Appendix 6)**
Rationale: Clarify study days of Screening during the Baseline Period.	
Original Text	**Amendment Text**
Table 1: Schedule of Assessments a: The Baseline Period is comprised of the initial screening for the study	Table 1: Schedule of Assessments a: The Baseline Period is comprised of the initial screening for the study and

and the assessment of baseline seizure activity recorded daily in the diary. Table 6: Time Windows for Assessments Visit 1 (Clinic; Study Day -42 to -41):	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).** Table 6: Time Windows for Assessments Visit 1 (Clinic; Study Day **-43 to -42 or** -42 to -41):
Rationale: Collection of blood sample for epilepsy genotype panel is mandatory but not required at screening.	
Original Text	**Amendment Text**
Table 1: Schedule of Assessments Epilepsy genotype panel X	Table 1: Schedule of Assessments Epilepsy genotype panel X[1] **1. Mandatory one time collection any time during or after screening.**
Rationale: Added the list of countries in which Diacomit® (stiripentol) is approved.	
Original Text	**Amendment Text**
Section 1.1.1, Existing Treatment for Dravet Syndrome To date, only one treatment, Diacomit® (stiripentol) is approved, and only in Europe as adjunctive therapy in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome), and must be co-administered with clobazam and valproate. Stiripentol has not been approved for use in the United States of America, but is available under compassionate use protocols at certain clinical sites.	Section 1.1.1, Existing Treatment for Dravet Syndrome To date, only one treatment, Diacomit® (stiripentol) is approved, and only in Europe, **Canada, Japan, and Australia**, as adjunctive therapy in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome), and must be co-administered with clobazam and valproate. Stiripentol has not been approved for use in the United States of America, but is available under compassionate use protocols at certain clinical sites.
Rationale: Added a supporting reference to an existing citation of data.	
Original Text	**Amendment Text**
Section 1.5, Existing Treatment for 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 treatment of DS; the efficacy and safety of this therapeutic approach have been published in a peer reviewed journal and reported to be very favorable. There are no treatments specifically approved for the treatment of DS in the United States of America (USA). Accordingly, there remains an unmet need for an approved treatment for children with DS.	Section 1.1.1, Existing Treatment for 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 treatment of DS; the efficacy and safety of this therapeutic approach have been published in a peer reviewed journal (**Ceulemans 2012; Ceulemans 2016**) and reported to be very favorable. There are no treatments specifically approved for the treatment of DS in the United States of America (USA). Accordingly, there remains an unmet need for an approved treatment for children with DS.
Rationale: Revised the preclinical data section.	
Original Text	**Amendment Text**
Section 1.3, Preclinical Data The pharmacokinetics of fenfluramine, norfenfluramine and their respective isomers has been studied in mice, rats, dogs and humans. The pharmacokinetics 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	Section 1.3, Preclinical Data The pharmacokinetics of fenfluramine, norfenfluramine and their respective isomers has been studied in mice, rats, dogs and humans. The pharmacokinetics 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 pharmacokinetics and metabolism

pharmacokinetics and metabolism of fenfluramine after oral administration. In humans, fenfluramine is metabolized to norfenfluramine. CYP2C19 and CYP2D6 appear to be the predominant CYP enzymes that metabolize fenfluramine to norfenfluramine. CYP1A2, CYP2B6 and CYP3A4/5 also appear to be involved, but to a lesser degree. In vitro inhibition and induction studies show that both fenfluramine and norfenfluramine cause inhibition of CYP2D6, while fenfluramine causes induction of CYP3A4 and CYP2B6. Based on the FDA's mechanistic static model, ZX008 is predicted to potentially cause clinically significant inhibition of CYP2D6 in the range of doses that will be administered (ZX008 IB 2016). ZX008 is also predicted to cause a clinically significant induction of CYP3A4 in most of the doses that will be administered. The major metabolite norfenfluramine, however, is not expected to cause clinically significant inhibition or induction of CYP2B6, 2D6 or 3A4. In vitro inhibition and induction studies show that both fenfluramine and norfenfluramine cause inhibition of CYP2D6, while fenfluramine causes induction of CYP3A4 and CYP2B6. Based on the FDA's mechanistic static model, ZX008 is predicted to potentially cause clinically significant inhibition of CYP2D6 in the range of doses that will be administered (ZX008 IB 2016). ZX008 is also predicted to cause a clinically significant induction of CYP3A4 in most of the doses that will be administered. The major metabolite norfenfluramine, however, is not expected to cause clinically significant inhibition or induction of CYP2B6, 2D6 or 3A4.	of fenfluramine after oral administration. In humans, fenfluramine is metabolized to primarily norfenfluramine. ~~CYP2C19~~**CYP1A2, CYP2B6,** and CYP2D6 appear to be the predominant CYP 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 nordexfenflurmaine (7%-8%) from the body. Because fenfluramine and its active metabolite norfenfluramine have multiple pathways of elimination, interference with a single pathway is unlikely to cause a significant change in fenfluramine's clearance though the probability of an interaction increases if multiple elimination mechanisms are affected simultaneously. ~~In vitro inhibition and induction studies show that both fenfluramine and norfenfluramine cause inhibition of CYP2D6, while fenfluramine causes induction of CYP3A4 and CYP2B6. Based on the FDA's mechanistic static model, ZX008 is predicted to potentially cause clinically significant inhibition of CYP2D6 in the range of doses that will be administered (ZX008 IB 2016). ZX008 is also predicted to cause a clinically significant induction of CYP3A4 in most of the doses that will be administered. The major metabolite norfenfluramine, however, is not expected to cause clinically significant inhibition or induction of CYP2B6, 2D6 or 3A4.~~ **While in vitro studies showed that both fenfluramine and norfenfluramine cause weak inhibition of CYP2D6 and fenfluramine causes weak induction of CYP3A4 and CYP2B6, further analysis based on the FDA's mechanistic static model shows that fenfluramine and its major metabolite norfenfluramine are unlikely to alter the pharmacokinetics of substrates of these CYP450 enzymes in the range of ZX008 doses that will be administered in this study.**
Rationale: Added a supporting reference to an existing citation of data.	
Original Text	**Amendment Text**
Section 1.5, Rationale for Current Study Based on several published reports of fenfluramine's successful treatment of refractory childhood epilepsy in the 1980s (Aicardi and Gaustaut 1985; Aicardi 1988) and its successful treatment of 11 refractory pediatric epilepsy patients in Belgium (Boel 1996), in 2002 Drs. Ceulemans and Lagae were granted authorization to prescribe fenfluramine to their patients with refractory pediatric epilepsy conditions, including DS, under an approved protocol under a Belgium	Section 1.5, Rationale for Current Study Based on several published reports of fenfluramine's successful treatment of refractory childhood epilepsy in the 1980s (Aicardi and Gaustaut 1985; Aicardi 1988) and its successful treatment of 11 refractory pediatric epilepsy patients in Belgium (Boel 1996), in 2002 Drs. Ceulemans and Lagae were granted authorization to prescribe fenfluramine to their patients with refractory pediatric epilepsy conditions, including DS, under an approved protocol under a Belgium government program

government program (Royal Decree). To date, these pediatric neurologists have DS patients (infants, children, young adults, and now also adults), being successfully treated with fenfluramine for over 27 years. The efficacy and safety of this therapeutic approach has been reported to be overwhelmingly favorable. In the most recent assessment of efficacy of these patients reported by the investigators in, the average length of treatment was over 12 years, with one patient being successfully treated for 26 years. Of the 15 DS treated patients, 10 (67%) were reported as seizure-free, with the average time of seizure-freedom being 6 years (range 1-19 years). Twelve patients (87%) had a greater than 90% reduction in seizure frequency and 14 patients (93%) with greater than 70% reduction in seizure frequency.	(Royal Decree). To date, these pediatric neurologists have DS patients (infants, children, young adults, and now also adults), being successfully treated with fenfluramine for over 27 years. The efficacy and safety of this therapeutic approach has been reported to be overwhelmingly favorable. In the most recent assessment of efficacy of these patients reported by the investigators in, the average length of treatment was over 12 years, with one patient being successfully treated for 26 years (**Ceulemans 2016**). Of the 15 DS treated patients, 10 (67%) were reported as seizure-free, with the average time of seizure-freedom being 6 years (range 1-19 years). Twelve patients (87%) had a greater than 90% reduction in seizure frequency and 14 patients (93%) with greater than 70% reduction in seizure frequency.
Rationale: Clarified the safety objective.	
Original Text	**Amendment Text**
Synopsis and Section 2.4, Safety Objective To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day to placebo with regard to AEs, laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate [HR], temperature, and respiratory rate), ECGs, ECHOs, and body weight. Cognitive Function will be assessed in subjects 5 years and older using the cognition domain score on the QOLCE. Cognitive function will be assessed using age-appropriate versions of the BRIEF.	Synopsis and Section 2.4, Safety Objective To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day to placebo with regard to AEs, laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate [HR], temperature, and respiratory rate), ECGs, ECHOs, and body weight. **Cognitive Function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the BRIEF.** ~~Cognitive Function will be assessed in subjects 5 years and older using the cognition domain score on the QOLCE. Cognitive function will be assessed using age-appropriate versions of the BRIEF.~~
Rationale: Clarify that the number of participating study centers is approximately 30.	
Original Text	**Amendment Text**
Section 3.4, Number of Study Centers The study expects to use up to 30 research centers in North America. Additional study centers within or outside of North America may be added if enrollment cannot be completed in a timely manner.	Section 3.4, Number of Study Centers The study expects to use up to **approximately** 30 research centers in North America. Additional study centers within or outside of North America may be added if enrollment cannot be completed in a timely manner.
Rationale: Clarified the duration of use of contraception after the last dose of study drug and added barrier method to the list of acceptable methods of birth control.	
Original Text	**Amendment Text**
Section 4.4 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 effective contraception from the time of informed consent until 90 days after study discharge. Female subjects who are sexually active and are of	Section 4.4 Male subjects who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception from the time of informed consent until 90 days **after the last dose of study drug** ~~after study discharge~~. 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 30 days following the last follow up visit. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: Progestogen-only hormonal contraception associated with inhibition of ovulation	childbearing potential must use, with their partner, an approved method of highly effective contraception from the time of informed consent until ~~30 days following the last follow up visit~~ **90 days after the last dose of study drug**. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation **and a barrier method (i.e., condom for male partner)**: Progestogen-only hormonal contraception associated with inhibition of ovulation **and a barrier method (i.e., condom for male partner)**:
Rationale: Removal of social media policy.	
Original Text	**Amendment Text**
Section 4.5 The subject or members of the subject's immediate family (including grandparents) violate the Social Media policy as described in Section 4.9. Section 4.9 Revelations about clinical trial participation and the effect(s) of unapproved study medications can influence the expectations of potential new study subjects and investigators. Throughout their participation in this trial, subjects, their parent/caregivers and immediate family members, including grandparents, can acknowledge participation in the study on social media; however, they will be required not to divulge suspected or actual IMP (ZX008 or placebo), dose, efficacy, or tolerability as it can negatively affect the sponsor's ability to interpret study results and possibly to use the study for registration. Individuals with serious and/or repeated violations of this policy may be required to exit the study at the discretion of the sponsor in consultation with the principal investigator, without the possibility of entering the separate open-label extension study.	Section 4.5 ~~The subject or members of the subject's immediate family (including grandparents) violate the Social Media policy as described in Section 4.9.~~ Section 4.9 ~~Revelations about clinical trial participation and the effect(s) of unapproved study medications can influence the expectations of potential new study subjects and investigators. Throughout their participation in this trial, subjects, their parent/caregivers and immediate family members, including grandparents, can acknowledge participation in the study on social media; however, they will be required not to divulge suspected or actual IMP (ZX008 or placebo), dose, efficacy, or tolerability as it can negatively affect the sponsor's ability to interpret study results and possibly to use the study for registration. Individuals with serious and/or repeated violations of this policy may be required to exit the study at the discretion of the sponsor in consultation with the principal investigator, without the possibility of entering the separate open-label extension study.~~
Rationale: Revised the prohibited concomitant medication and foods list, including Appendix 1.	
Original Text	**Amendment Text**
Section 5.7.4 Drugs/foods that potentially interact with ZX008 via the CYP2D6, CYP3A4, and/or CYP2B6 pathways: 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.	Section 5.7.4 ~~Drugs/foods that potentially interact with ZX008 via the CYP2D6, CYP3A4, and/or CYP2B6 pathways:~~ 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. Appendix 1: replaced, edits not shown herein.

Appendix 1: replaced, edits not shown herein.	
Rationale: Clarify the timing of procedures during the baseline period and screening period.	
Original Text	**Amendment Text**
Section 6.1 The Baseline Period of the study encompasses the screening activities that will occur on Study Day -42 and Study Day -41 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. With the exception of the Doppler ECHO, which may be completed any time during the Baseline Period up to Study Day -21, all screening assessments will be completed on Study Day -42 and Study Day -41. The following procedures will be performed during the Screening visit, which will occur between Study Day -42 and Study Day -41 for all subjects before the start of seizure activity observation:	Section 6.1 The Baseline Period of the study encompasses the screening activities that will occur on Study Day -42 ~~and Study Day -41~~ 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. ~~With the exception of the Doppler ECHO, which may be completed any time during the Baseline Period up to Study Day -21, all screening assessments will be completed on Study Day -42 and Study Day -41.~~ ~~The following procedures will be performed during the Screening visit, which will occur between Study Day -42 and Study Day -41 for all subjects before the start of seizure activity observation:~~ **The Screening visit will occur on Study Day -42; however, the procedures may be split over 2 consecutive days (e.g., 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:**
Rationale: Added text clarifying procedures for rescreening.	
Original Text	**Amendment Text**
Section 6.1.1 None.	Section 6.1.1 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 re-screened 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.
Rationale: Clarify timing of dosing on Day -1 and Day 1.	
Original Text	**Amendment Text**
Section 6.1.3 • Dispense study medication Section 6.2.1 Subjects will begin dosing with IMP in the morning of Titration Period Study Day 1.	Section 6.1.3 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.) Section 6.2.1 Subjects will take their first dose of study medication on the morning of Study Day 1. Study Day 1 is considered the first day of dosing, even for those subjects that received an in-clinic dose on Study Day -1. ~~Subjects will begin dosing with IMP in the morning of Titration Period Study Day 1.~~
Rationale: Revised estimated blood volume collection in Table 8 and text describing volumes for collection.	
Original Text	**Amendment Text**
Section 6.5 The original Table 8 was replaced; edits to this table are not shown herein. The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately 108.7 mL, as outlined in Table 8	Section 6.5 The original Table 8 was replaced; edits not shown herein. A new table, Table 9, showing the priorities for blood collection was added. The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately ~~108.7~~ **99.7** mL, as outlined in Table 8. ***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 43/Visit 8 the pharmacokinetic 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 9:**
Rationale: Clarification of SE as an AE or SAE.	
Original Text	**Amendment Text**
Section 7.1.1 Seizures that evolve into SE will be captured by type and duration (>10 min) as are all seizures. The diagnosis of SE 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. 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	Section 7.1.1 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 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 (e.g. 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.
Rationale: Clarify SAE reporting.	
Original Text	**Amendment Text**

Section 8.6 For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the AE page of the eCRF. An electronic document containing the AE page and other applicable pages of the eCRF must be sent (via facsimile or email) to the sponsor together with a **Notification of Serious Adverse Event at Investigator Site** cover page, which has been signed and dated by the investigator. If an electronic document is not able to be generated (eg, internet access problem), a handwritten paper SAE report must be completed, which must be signed and dated by the investigator. All SAEs that occur during the course of the study, whether or not causally related to IMP must be reported immediately via telephone and either facsimile or email (within 24 hours of the investigator becoming aware of the event) to the sponsor and the Medical Monitor.	Section 8.6 ~~For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the AE page of the eCRF. An electronic document containing the AE page and other applicable pages of the eCRF must be sent (via facsimile or email) to the sponsor together with a **Notification of Serious Adverse Event at Investigator Site** cover page, which has been signed and dated by the investigator. If an electronic document is not able to be generated (eg, internet access problem), a handwritten paper SAE report must be completed, which must be signed and dated by the investigator.~~ In the event of a 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 iHC 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
Rationale: To evaluate a correlation between study drug and SAE.	
Original Text	**Amendment Text**
Section 8.9 None.	Section 8.9 **In the event of a SAE a blood sample for ZX008 and AED PK should be collected as soon as feasible.**

Clinical Study Protocol

Study Title:	A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome
Study Number:	ZX008-1502
Study Product:	Fenfluramine Hydrochloride Oral Solution; ZX008
IND Number:	125797
EudraCT Number:	2015-004167-37
Sponsor:	Zogenix International Limited A wholly owned subsidiary of Zogenix, Inc. 5858 Horton Street, Suite 455 Emeryville, CA 94608 USA
Sponsor's Medical Contact	[redacted]
Date of Study Protocol:	31 October 2016 (Protocol Amendment 2.0) 11 January 2016 (Protocol Amendment 1) 30 October 2015 version 1.0 (Original Protocol)

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: ZX008-1502

Study Title: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

Sponsor's Responsible Officer: Gail M. Farfel, PhD
Director

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Signature

2Nov2016

Date (Day/Month/Year)

SIGNATURE OF COORDINATING INVESTIGATOR

Study Number: ZX008-1502

Study Title: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Adolescents with Dravet Syndrome

Coordinating Investigator: Lieven Lagae, MD, PhD

Leuven University
Department of Development and Regeneration
Section Pediatric Neurology
Leuven, Belgium

Signature [redacted]

Date (Day/Month/Year)

02 NOV 2016

SIGNATURE(S) OF PRINCIPAL INVESTIGATOR(S)

Study Number: ZX008-1502

Study Title: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

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
ANCOVA	analysis of covariance
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
BRIEF	Behavior Rating Inventory for Executive Function
C-SSRS	Columbia-Suicide Severity Rating Scale
CBD	cannabidiol
CFR	Code of Federal Regulations
C_{max}	Maximum observed concentration determined directly from the concentration-time profile
CYP	cytochrome P450
dL	Deciliter
DS	Dravet syndrome
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	electronic Case Report Form
EOS	End of study
EPAR	European Public Assessment Report
EQ-5D-5L	Standardized measure of health status
ET	Early Termination
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GH	Growth Hormone
GMP	Good Manufacturing Practices
HADS	Hospital Anxiety and Depression Scale
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDSMC	Independent Data and Safety Monitoring Committee
IEC	Independent Ethics Committee
IGF-1	Insulin-like Growth Factor-1
IMP	Investigational Medicinal Product
IPCAB	International Pediatric Cardiology Advisory Board
IRB	Institutional Review Board
ABBREVATION	DEFINITION
IU	International Unit

ABBREVATION	DEFINITION
IVR	Interactive Voice Response
IWR	Interactive Web Response (System)
KD	Ketogenic diet
kg	Kilogram
LH	Luteinizing Hormone
MCSF	Mean Convulsive Seizure Frequency
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/kg/day	milligram per kilogram per day
min	Minutes
mITT	modified Intent-to-Treat
mL	Milliliter
PedsQL	Pediatric Quality of Life Inventory
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
SD	Standard Deviation
SMEI	Severe Myoclonic Epilepsy Of Infancy
SUDEP	Sudden Unexpected Death in Epilepsy
T+M	Titration plus Maintenance Periods
t1/2	terminal half-life
THC	tetrahydrocannabinol
Tmax	time to maximum concentration
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
USA	United States of America
USP	United States Pharmacopeia
VNS	Vagal Nerve Stimulator/Stimulation
ZX008	Fenfluramine Hydrochloride Oral Solution

STUDY SYNOPSIS

Study Title: A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome	
Study Number: ZX008-1501	
Study Product: Fenfluramine Hydrochloride Oral Solution, ZX008	
Type of Study: Efficacy, safety, and pharmacokinetics study	**Indication Studied:** Adjunctive therapy in Dravet syndrome
Phase of Development: Phase III	**Countries**: Europe, Australia, South Korea
Sponsor: Zogenix International Limited	
Coordinating Investigator: Lieven Lagae, MD, PhD Leuven University, Department of Development and Regeneration, Section Pediatric Neurology Leuven, Belgium	
Estimated Duration of Individual Subject Participation: The duration of the participation in the study for an individual subject is expected to be up to 22 weeks, with a follow-up 3 to 6 months after the last dose of study medication for final safety monitoring.	

Objectives:

The primary objective of the study is:

- To demonstrate that ZX008 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment 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).

The key secondary objectives of the study are:

- To demonstrate that ZX008 0.2 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome based on change in the frequency of convulsive seizures between baseline and T+M.
- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) 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.

See Statistical Methods (Section 10.5.1.3) for hierarchical testing procedure. Additional secondary efficacy objectives of the study are:

- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) 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.

- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints:
  - Clinical Global Impression – Improvement rating, as assessed by the principal investigator.
  - Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver.
  - The change from baseline in the Quality of Life in Childhood Epilepsy (QOLCE) score to measure quality of life.
  - The change from baseline in the Pediatric Quality of Life Inventory™ (PedsQL) score.
  - The change from baseline in PedsQL Family Impact module score.
  - The change from baseline in the quality of life (QoL) of the parent/caregiver using the EQ- 5D-5L scale.
  - The change from baseline in affective symptoms of the parent/caregiver using the Hospital Anxiety and Depression Scale (HADS).

The safety objective of the study is:

- To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day 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), and body weight. Cognitive Function will be assessed in subjects 5 years and older using the cognition domain score on the QOLCE. Cognitive function will be assessed using and age-appropriate versions of the BRIEF

The pharmacokinetics (PK) objective of the study is:

- To characterize the PK of ZX008 0.2 and 0.8 mg/kg/day at steady state in subjects ages 2-6 years and ≥6-18 years with Dravet syndrome.

The exploratory objectives of the study are:

- To compare the ZX008 0.2 and 0.8 mg/kg/day doses on primary, secondary, safety and PK endpoints.

Methodology:

This is a multicenter, double-blind, parallel-group, placebo-controlled, study to assess the efficacy, safety, and PK of ZX008 when used as adjunctive therapy in pediatric and young adult subjects with Dravet syndrome. Approximately 30 study sites in Europe, Australia, and South Korea are planned to participate. 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 (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 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 over a 14-day Titration Period. Following titration, subjects will continue treatment at their randomly assigned dose over a 12-week Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is 14 weeks. At the end of the Maintenance Period (or early discontinuation), all subjects will undergo a 2-week taper or transition period (Post-Dosing Follow-Up) depending on whether they exit the study or are enrolled in the separate long-term open-label extension study. 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 study.

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 1.

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.

Number of Subjects:

Approximately 130 subjects will be screened to obtain 115 subjects who enter the Baseline Period. Of these 115 subjects, it is estimated that 105 subjects will be randomized into the Titration Period. Each clinical site will not randomize more than a maximum of 10 subjects without prior consent from the sponsor.

Inclusion Criteria: All 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 last 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 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, tonic-atonic, tonic-clonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.
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 has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
8. Subject has provided assent in accordance with Institutional Review Board (IRB) requirements, if capable.
9. Subject's parent/caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.

Exclusion Criteria: All subjects must meet none of the following exclusion criteria to 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 is at imminent risk of self-harm or harm to others, in the investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must be excluded if they report suicidal behavior in the past 6 months as measured by the C-SSRS at Screening or Baseline, which includes suicidal ideation with intent and plan (Item #5). If a subject reports suicidal ideation on Item 4 without specific plan, and the investigator feels that the subject is appropriate for the study considering the potential risks, the investigator must document appropriateness for inclusion, and discuss with the parent/caregiver to be alert to mood or behavioral changes, especially around times of dose adjustment.
6. Subject has a current or past history of glaucoma.

7. Subject has moderate or severe hepatic impairment. 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.
8. Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine- oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; or cyproheptadine (see Appendix 1). (Note: Short- term medication requirements will be handled on a per case basis by the Medical Monitor.)
9. Subject is currently receiving or has received stiripentol in the past 21 days prior to Screening.
10. Subject is currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy.
11. 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.
12. Subject has positive result on urine tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at the Screening Visit.
13. Subject has participated in another clinical trial within the past 30 days.
14. Subject is currently receiving an investigational product.
15. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
16. 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: Subjects must meet all of the inclusion criteria above plus the following criteria, to be randomized:

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 3 weeks.
4. Subject's parent/caregiver has been compliant with diary completion during the Baseline Period, in the opinion of the investigator (e.g., at least 90% compliant).

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. Subjects

will be randomized to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 mg/day) or placebo. Study medication will be administered twice a day (BID) in equally divided doses with food.

Reference Product, Dose, and Mode of Administration:
Matching ZX008 placebo is supplied as an oral solution.

Duration of Treatment:
All subjects will receive ZX008 or matching placebo for up to approximately 16 weeks (Titration Period=2 weeks; Maintenance Period=12 weeks; Taper/Transition Period=2 weeks). After completion of the Maintenance Period, eligible subjects may enroll in the open-label extension study, after completion of the transition. Subjects who do not enroll in the open-label extension study will undergo a taper off of study medication (doses will be administered in a blinded fashion similar to the titration, i.e., doses will be decreased in 4-day increments). 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:
Efficacy:

- Number of seizures by type
- Convulsive seizure-free interval
- Clinical Global Impression – Improvement as assessed by parent/caregiver
- Clinical Global Impression – Improvement as assessed by principal investigator
- QOLCE to measure changes in quality of life of the subject
- PedsQL to measure changes in quality of life of the subject
- PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver
- QoL of parent/caregiver using the EQ-5D-5L scale
- Affective symptoms of parent/caregiver using the HADS scale
- Duration of prolonged seizures (seizure type that, during baseline, had duration >2 minutes)
- Number of episodes of status epilepticus
- Number of instances of rescue medication use and number of doses
- Number of inpatient hospital admissions due to seizures

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. The BRIEF will be administered to track cognitive function.
Pharmacokinetics:
Steady-state plasma fenfluramine PK parameters (maximum observed concentration determined directly from the concentration time profile [C_{max}], area under the concentration time curve from time zero to time=t [AUC_{0-t}], time to maximum concentration [T_{max}], and terminal half-life [$t_{1/2}$]) after administration of ZX008 derived using population PK methods.

Sample Size Determination:
The results of the only randomized, placebo-controlled studies in subjects with Dravet syndrome can be found in the European Public Assessment Report (EPAR) for stiripentol (EMA, 2007). The EPAR summarizes the results from two studies: STICLO France and STICLO Italy. In the

stiripentol 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 0.8 mg/kg/day 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. Similar assumptions and calculations yield a requirement for an additional 35 subjects in the 0.2 mg/kg/day ZX008 group. Thus, the total sample size is planned to be 105 subjects (35 per arm).

Statistical Methods:

Study Populations:

Safety Population: All safety analyses will be performed on the Safety Population defined as all randomized subjects who receive at least one dose of study medication. Subjects will be analyzed according to the treatment actually received.

Modified Intent-to-Treat (mITT) Population: The mITT Population is defined as all randomized subjects who receive at least one dose of study medication and for whom at least 1 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 0.8 mg/kg/day to placebo as well as key secondary efficacy assessments will be performed on the mITT Population.

Per Protocol (PP) Population: The PP Population is defined as all randomized subjects who receive at least one dose of ZX008 or placebo, complete the Maintenance Period, and have no major protocol violations that would have a significant impact on clinical outcome.

Efficacy

Primary Efficacy Analysis: 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 (three levels) and age group (< 6 years, ≥6 years) as factors, and with Baseline MCSF as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day 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 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 echocardiogram, C-SSRS, Tanner Staging results, etc, will be summarized appropriately, by treatment. All safety summaries will be based on the Safety Population.

Pharmacokinetics

A population PK model will be fit to the fenfluramine concentration-time data collected during the Maintenance Period. This model will be informed by all relevant data available at the time of data collection (both adults and pediatrics). The population mean and interindividual variability estimates from the fit of the population PK model will be summarized. Derived plasma PK parameters (C_{max}, AUC_{0-t}, T_{max}, and $t_{1/2}$) will be summarized descriptively by treatment group and compared to historical data from adults. Summary statistics for plasma concentrations will be provided by PK sampling time.

Table 1: Schedule of Assessments

Study Assessments	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Post-Dosing	Cardiac Follow-up
	Screening		Random-ization	Titration Period			Maintenance Period							
Visit Number	**1**	**2 (Phone)**	**3**		**4, 5 (Phone)**	**6**	**7 (Phone)**	**8**	**9 (Phone)**	**10**	**11 (Phone)**	**12**	**13**	**14**
Study Day	**-42**	**-21**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**197-281**
Informed Consent (subject and parent)	X													
Inclusion/Exclusion Criteria	X		X											
Demographics	X													
Medical/Neurological History	X													
Epilepsy history	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[c]
Neurological Examination, complete	X											X		
Neurological Examination, abbreviated			X			X								
Vital signs	X		X			X		X		X		X		
Weight, Height, BMI	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	X[e]		X[e]			X[e]		X[e]		X[e]		X[e]		
Clinical laboratory evaluation (hematology/clinical chemistry/urinalysis, etc)	X		X			X		X		X		X		
Plasma sample for ZX008 pharmacokinetics								4X[f]						
Plasma sample for background AEDs			X[g]			X[g]		X[g]				X[g]		
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	R	C/R/D	R	C/R/D	R	C/R/D[h]	C/R	
Epilepsy genotype panel	X[l]													
Study Medication			D		R[i]	C/R/D	R	C/R/D	R	C/R/D	R	C/R/D[h]	C/R	
C-SSRS	X		X			X		X		X		X		

continued

Table 1: Schedule of Assessments (continued)

Study Assessments	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Follow -up[c]	Cardiac Follow-up
	Screening		Random-ization	Titration Period			Maintenance Period							
Visit Number	**1**	**2 (Phone)**	**3**		**4, 5 (Phone)**	**6**	**7 (Phone)**	**8**	**9 (Phone)**	**10**	**11 (Phone)**	**12**	**13**	**14**
Study Day	**-42**	**-21**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**197-281**
Clinical Global Impression - Improvement (assessed by parent/caregiver)						X		X		X		X		
Clinical Global Impression - Improvement (assessed by principal investigator)						X		X		X		X		
BRIEF			X					X				X		
QOLCE			X					X				X		
PedsQL			X					X				X		
EQ-5D-5L (QoL of parent/caregiver)			X									X		
HADS (Affect of parent/caregiver)			X					X				X		
Randomize subject			X											
First Day of Study Drug Administration				X[j]										
Daily Diary Completion	X													
Concomitant Medication				X										
Adverse events	X													
Adverse events of special interest	X													X[k]

AED=antiepileptic drug; BMI=body mass index; C=Collect; CBD=cannabidiol; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination; EQ-5D-5L=standardized measure of health status; HADS=Hospital Anxiety and Depression Scale; QoL=quality of life; BRIEF-P=Behavior Rating Inventory of Executive Function, Preschool version; QOLCE=Quality of Life in Childhood Epilepsy; R=Review

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 an up to 2-week period.

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 study (see Section 6.4).

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 pharmacokinetic assessment will be conducted prior to the dose at Visit 8 and 1, 2, and 4-6 hours after dose administration.

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 study 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.

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 (DS).

DS, 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 (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. Dravet children 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 DS 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

DS 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 DS 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, and only in Europe, Canada, Japan, and Australia, as adjunctive therapy in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome), and must be co-administered with clobazam and valproate. Stiripentol has not been approved for use in the United States of America, but is available under compassionate use protocols at certain clinical sites.

[redacted] 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 treatment of DS; the efficacy and safety of this therapeutic approach have been published in peer reviewed journal

(Ceulemans 2012; Ceulemans 2016) and reported to be very favorable. There are no treatments specifically approved for the treatment of DS in the United States of America (USA). Accordingly, there remains an unmet need for an approved treatment for children with DS.

1.1.2 Other Antiepileptic Medications

USA and European Union approved anti-epileptic drug products include valproate, topiramate, carbamazepine, oxcarbazepine, lamotrigine, benzodiazepines, phenobarbital, potassium bromide, ethosuximide, phenytoin, and vigabatrin. The treatment of DS 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 DS. In fact, some commonly used anti- epileptic drugs with a sodium channel mechanism of action, such as carbamazepine, oxcarbazepine, phenytoin, and lamotrigine, make DS worse.

A review of the treatment modalities used for DS has been published by Chiron and Dulac (Chiron and Dulac 2011). This review indicates that valproate 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 the benefit of these compounds is mild and there are no trials to validate the impression of any effect.

Given the cognitive consequences believed to be caused, at least in part, by frequent childhood seizure activity, there is a medical need for a new anticonvulsant treatment that can significantly reduce seizure activity in DS. There is the possibility that early, effective seizure control could be disease-modifying, leading to an improvement in longer-term outcomes with respect to motor impairment, behavioral issues, and cognitive function.

1.2 BACKGROUND INFORMATION ON STUDY PRODUCT

Zogenix is developing a new formulation of fenfluramine hydrochloride, ZX008, for the adjunctive treatment of DS. Fenfluramine is an amphetamine analogue that was first synthesized many years ago. It was approved in a large number of countries and widely prescribed as an appetite suppressant for the treatment of adult obesity. Brand names for fenfluramine formulations included Ponderax, Pondimin and others. Fenfluramine was also used extensively in an off-label combination with phentermine ("Fen-Phen"). Fenfluramine is a racemic compound and the single enantiomer D-fenfluramine (dexfenfluramine) was also approved and marketed as Adifax, Redux, and others.

Fenfluramine was introduced in the USA in 1973. Products containing fenfluramine and D-fenfluramine were withdrawn from the USA market in 1997 after reports of heart valve disease and pulmonary hypertension (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 DS 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 of fenfluramine, norfenfluramine and their respective isomers has been studied in mice, rats, dogs and humans. The pharmacokinetics 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 pharmacokinetics and metabolism of fenfluramine after oral administration. In humans, fenfluramine is metabolized primarily to norfenfluramine. CYP1A2, CYP2B6 and CYP2D6 appear to be the predominant CYP 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 nordexfenflurmaine (7%-8%) from the body. Because fenfluramine and its major metabolite norfenfluramine have multiple pathways of elimination, interference with a single pathway is unlikely to cause a significant change in fenfluramine's clearance though the probability of an interaction increases if multiple elimination mechanisms are affected simultaneously.

While in vitro studies showed that both fenfluramine and norfenfluramine cause weak inhibition of CYP2D6 and fenfluramine causes weak induction of CYP3A4 and CYP2B6, further analysis based on the FDA's mechanistic static model shows that fenfluramine and its major metabolite norfenfluramine are unlikely to alter the pharmacokinetics of substrates of these CYP450 enzymes in the range of ZX008 doses that will be administeredin 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 equivalent to a human dose of 1.94 mg/kg/day based on body surface area, and provides a safety factor of 2.4 for the highest dose of 0.8 mg/kg/day that will be administered clinically.

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

Based on several published reports of fenfluramine's successful treatment of refractory childhood epilepsy in the 1980s (Aicardi and Gaustaut 1985; Aicardi 1988) and its successful treatment of 11 refractory pediatric epilepsy patients in Belgium (Boel 1996), in 2002 Drs.

Ceulemans and Lagae were granted authorization to prescribe fenfluramine to their patients with refractory pediatric epilepsy conditions, including DS, under an approved protocol under a Belgium government program (Royal Decree). To date, these pediatric neurologists have DS patients (infants, children, young adults, and now also adults), being successfully treated with fenfluramine [redacted] The efficacy and safety of this therapeutic approach has been reported to be overwhelmingly favorable. In the most recent assessment of efficacy of these patients reported by the investigators in 2016, the average length of treatment was over 12 years, with one patient being successfully treated for 26 years (Ceulemans 2016). Of the 15 DS treated patients, 10 (67%) were reported as seizure-free, with the average time of seizure-freedom being 6 years (range 1-19 years). Twelve patients (87%) had a greater than 90% reduction in seizure frequency and 14 patients (93%) with greater than 70% reduction in seizure frequency.

In addition, numerous publications discuss the use of fenfluramine in over 500 children with neurobehavioral conditions for the treatment of mostly autism and ADHD, without any reports of any cardiovascular adverse events (ZX008 IB 2016).

Prior to being withdrawn from the market, fenfluramine was marketed at doses of 20 mg and 40 mg three times daily for the management of obesity in adults. The doses tested thus far in DS range from 0.12 to 0.9 mg/kg/day in subjects over 1 year of age to adults. Doses tested in pediatric studies evaluating autism and ADHD ranged from 0.65 mg/kg/day to 3.6 mg/kg/day, but a commonly used dose was 1.5 mg/kg/day. Occasionally, fixed doses of 30 to 80 mg were used. The PK exposure associated with the proposed doses in DS studies of 0.2 mg/kg/day and

0.8 mg/kg/day administered orally (in equally divided doses BID) is expected to be lower than that obtained at the doses used in the past for the treatment of obesity in adults and of neurobehavioral conditions in children and adolescents (ZX008 IB 2016). The doses used in this study are based on the data from the DS patients being successfully treated in Belgium discussed above.

There are no treatments specifically approved for the treatment of DS in the USA, and in fact, commonly used anticonvulsants with a sodium channel mode of action, such as phenytoin and carbamazepine, worsen the condition. Accordingly, there remains a significant unmet need for an approved treatment for children and adults with DS.

1.6 RISK-BENEFIT ASSESSMENT

As described above, fenfluramine has been used successfully for up to 27 years in some DS patients to control seizures, without emergence of clinical valvulopathy or pulmonary hypertension. Fenfluramine was administered to over 500 children with neurobehavioral

conditions, including autism and ADHD with good safety and tolerability, most often at a 1 mg/kg dose.

The pharmacologic and toxicological profile for the active pharmaceutical ingredient, fenfluramine, following oral administration is well established (see ZX008 IB 2016).

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

The approximate volume of blood (108.7 mL) planned for collection from each subject over the course of the entire study (Screening to End of Study, but not including repeat or additional tests ordered by the investigator) presents no undue risk to the subjects.

The ZX008 0.2 mg/kg/day and 0.8 mg/kg/day doses are believed to be therapeutic doses, which could provide sufficient anti-epileptic support for a sustained period of time during the study.

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

The primary objective of the study is:

- To demonstrate that ZX008 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment 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).

2.2 KEY SECONDARY OBJECTIVES

The key secondary objectives of the study are:

- To demonstrate that ZX008 0.2 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of Dravet syndrome based on change in the frequency of convulsive seizures between baseline and T+M.
- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) 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.

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

2.3 ADDITIONAL SECONDARY OBJECTIVES

Other secondary objectives of the study are:

- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints:
    - The number of convulsive seizure-free days.
    - The proportion of subjects who achieve ≥75% reduction 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.
- To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints:
    - Clinical Global Impression – Improvement rating, as assessed by the principal investigator.
    - Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver.
    - The change from baseline in the QOLCE score.
    - The change from baseline in the PedsQL score.
    - The change from baseline in the PedsQL Family Impact module score.
    - The change from baseline in the QoL of the parent/caregiver using the EQ-5D-5L scale.
    - The change from baseline in the affective symptoms of the parent/caregiver using the HADS.

2.4 SAFETY OBJECTIVE

The safety objective of the study is:

- To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day to placebo with regard to AEs, laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate [HR], temperature, and respiratory rate), ECGs, ECHOs, and body weight Cognitive Function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the BRIEF.

2.5 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective of the study is:

- To characterize the PK of ZX008 0.2 and 0.8 mg/kg/day at steady state in subjects ages 2-6 years and >6-18 years with Dravet syndrome.

2.6 EXPLORATORY OBJECTIVE

The exploratory objective of the study is:

- To compare the ZX008 0.2 and 0.8 mg/kg/day doses on primary, secondary, safety and PK endpoints.

2.7 STUDY ENDPOINTS

2.7.1 Efficacy Endpoints

The efficacy endpoints of the study are:

- Number of seizures by type
- Convulsive seizure-free interval
- Clinical Global Impression – Improvement as assessed by parent/caregiver
- Clinical Global Impression – Improvement as assessed by principal investigator
- QOLCE to measure changes in quality of life of the subject
- PedsQL to measure changes in quality of life of the subject
- PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver
- QoL of the parent/caregiver using the EQ-5D-5L scale
- Affective symptoms of the parent/caregiver using the HADS scale
- Duration of prolonged seizures (seizure type that, during baseline, had duration >2 minutes)
- Number of episodes of status epilepticus
- Number of instances of rescue medication use and number of doses
- Number of inpatient hospital admissions due to seizures

2.7.2 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
- BRIEF to measure cognition

2.7.3 Pharmacokinetic Endpoints

The PK endpoints of the study are:

- Steady-state plasma fenfluramine PK parameters (C_{max}, AUC_{0-t}, T_{max}, and $t_{1/2}$) after administration of ZX008 derived using population PK methods

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This is a multicenter, double-blind, parallel-group, placebo-controlled, study to assess the efficacy, safety, and PK of ZX008 when used as adjunctive therapy in pediatric and young adult subjects with Dravet syndrome. Approximately 30 study sites in Europe, Australia, and South Korea are planned to participate. 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 (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 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 over a 14-day Titration Period. Following titration subjects will continue treatment at their randomly assigned dose over a 12-week Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is 14 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 1.

At the end of the Maintenance Period (or early discontinuation), all subjects will undergo a 2-week taper or transition period (Post-Dosing Follow-Up) depending on whether they exit the study or are enrolled in the separate long-term open-label extension study.

A follow-up ECHO, ECG, and possibly physical examination 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 study.

3.2 NUMBER OF SUBJECTS

Approximately 130 subjects will be screened to obtain 115 subjects who enter the Baseline Period. Of these 115 subjects, it is estimated that 105 subjects will be randomized into the Titration Period. Each clinical site will not randomize more than a maximum of 10 subjects without prior consent from the sponsor.

3.3 STUDY DURATION

The duration of participation in the study for an individual subject is expected to be up to

22 weeks, plus follow-up safety visit 3 to 6 months after the last dose:

- Baseline Period – 6 weeks
- T+M Period - 14 weeks
- Post-Dosing Visit – 2 weeks 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 study.

3.4 NUMBER OF STUDY CENTERS

The study expects to use up to approximately 30 research centers in Europe, Australia, and South Korea. Additional study centers within or outside of Europe, Australia, and South Korea may be added if enrollment cannot be completed in a timely manner.

3.5 RATIONALE FOR STUDY DESIGN AND CHOICE OF TREATMENT GROUPS

It is recognized that performing clinical studies in young children or in subjects with reduced cognitive capacity presents particular practical and ethical issues. However, given the seriousness of DS, and the possible consequences of current inadequate treatments, the use of children with DS in this study is considered justified. Stratifying the randomization 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 aged 6 -18 years. The study design has incorporated a titration period to enable subjects randomized to the high dose group adequate time to acclimate to this dose. 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.

Subjects will receive investigational medicinal product (IMP; 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. 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 will be able to receive ZX008 in an open-label extension study for up to 1 additional year of treatment.

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 6.2.9 and Section 6.3.

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)/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.

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

The IDMSC 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 pharmacokinetic data and any other data that may affect subject continuation.
- Make recommendations regarding the continuation, suspension, or termination of the study.

3.7.2 International Pediatric Cardiac Advisory Board (IPCAB)

The IPCAB is an advisory body to the sponsor that monitors cardiac safety of the ZX008 clinical trials and provides advice to the IDMSC. The IPCAB charter outlines the roles and responsibilities of the committee and guides its operations, and review of 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.). 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 adverse event, 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, member 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, as supplied by the sponsor.

4.1 INCLUSION CRITERIA

Subjects meeting all of the following inclusion criteria may 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 last 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 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, tonic-atonic, tonic-clonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.
6. All medications or interventions for epilepsy (including KD and VNS) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
7. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
8. Subject has provided assent in accordance with Institutional Review Board (IRB) requirements, if capable.
9. Subject's parent/caregiver is willing and able to be compliant with diary completion, visit schedule 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 is at imminent risk of self-harm or harm to others, in the investigator's opinion, based on clinical interview and/or responses provided on the C-SSRS. Subjects must be excluded if they report suicidal behavior in the past 6 months as measured by the C- SSRS at Screening or Baseline, which includes suicidal ideation with intent and plan (Item #5). If a subject reports suicidal ideation on Item 4 without a specific plan, and the investigator feels that the subject is appropriate for the study considering the potential risks, the investigator must document appropriateness for inclusion, and discuss with the parent/caregiver to be alert to mood or behavioral changes, especially around times of dose adjustment.
6. Subject has a current or past history of glaucoma.
7. Subjects with moderate or severe hepatic impairment may not be entered. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3xULN and/or elevated

bilirubin <2xULN) may be entered into the study after review and approval by the Medical Monitor in conjunction with the sponsor, with consideration of potential cause, concomitant medications, and other risk factors.

8. Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; or cyproheptadine (see Appendix 1). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)
9. Subject is currently receiving or has received stiripentol in the past 21 days prior to Screening.
10. Subject is currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy.
11. 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.
12. Subject has positive result on urine THC Panel or whole blood CBD at the Screening Visit.
13. Subject has participated in another clinical trial within the past 30 days.
14. Subject is currently receiving an investigational product.
15. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
16. 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

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

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 childbearing potential must use, with their partner, a condom plus 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)

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 (i.e., condom for male partner):
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation and a barrier method (i.e., 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 volunteer is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

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

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 IDMSC 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 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 IDMSC 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 6.2.9 and Section 6.3. 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

Enough subjects will be enrolled in the trial to ensure that approximately 105 subjects are randomized into the T+M Period. Randomized subjects will not be replaced.

4.8 ELIGIBILITY FOR EXTENSION STUDY

Subjects who complete the 12-week Maintenance Period of this study will be eligible to enroll in a planned, separate, open-label extension trial of ZX008 if they meet Inclusion/Exclusion criteria for that study regarding their suitability for continued participation in a trial of

fenfluramine.

Subjects must complete the entire 12-week Maintenance Period in order to be offered enrollment into the separate, open-label extension trial of ZX008. Those subjects who do not complete 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 study 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 study 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 2).

Table 2: 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

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 also will be provided. Doses to be studied include 0.2 mg/kg/day and

0.8 mg/kg/day divided into two daily (BID) doses, up to a maximum of 30 mg/day. An intermediate dose of 0.4 mg/kg/day will be used for titration. The concentration of ZX008 oral solution received by subjects (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) will be randomized across the 3 available concentrations in order to ensure blinding.

If the parent/caregiver is unable to administer the full dose due to spillage (eg, dose was spilled during measuring, subject spit dose out during administration), he/she should attempt to give the full dose noting the extra amount used to fulfill the dose. **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 Labeling and Packaging

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 Labeling and Packaging

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 (59-77°F) with excursions of 5-30°C (41-86°F) 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.

Assignment of ZX008 or placebo 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 drug accountability form provided by the sponsor before the start of the study. 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 Randomization

Upon completion of the Baseline Period, subjects who qualify for the study will be randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; 30mg/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 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 0.2 mg/kg/day, ZX008 0.8 mg/kg/day, 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.

5.5.2 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 (kg) at Visit 3 (Study Day -1). At Visit 8 (Study Day 43), if the subject's weight (kg) has changed ±25% of the weight at Study Day-1, the IMP dose will be recalculated. Subjects should be dosed using the oral dosing syringe provided.

In order to maintain the blind across all dose groups (Section 5.6) and allow step titration to the high dose, the dose for each subject will be titrated starting with a dose of ZX008 0.2 mg/kg/day (or placebo equivalent) BID. After 4 days at this dose level (Study Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group will increase their dose to 0.4 mg/kg/day (maximum 30 mg/day) while doses in the other two groups will remain constant. On Study Day 9, the dose for the 0.8 mg/kg/day group will increase to the target dose or a maximum of 30 mg/day. The titration is expected to take a total of 14 days (Table 3). A new bottle of IMP will be started by the subject at each level of the titration step. See Section 5.6 for more information about the volume of ZX008 or placebo to be administered.

Table 3 Titration Algorithm

Randomized Group	Titration Step 1 Study Day 1-4	Titration Step 2 Study Days 5-8	Titration Step 3 Study Days 9-14
ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.8 mg/kg/day
Placebo	Placebo	Placebo	Placebo
Note: maximum daily dose of ZX008 is 30 mg			

5.5.3 Maintenance Period

After completion of the Titration Period, subjects will enter the Maintenance Period and continue to receive the randomized dose of ZX008 or placebo and be treated for an additional 12 weeks. Study medication will continue to be administered BID in the morning and in the evening, approximately 12 hours apart, 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.

5.5.4 Taper Period

Subjects who complete the Maintenance Period and will not be continuing into the open-label extension study, and subjects who discontinue from the study early, will be tapered off of study medication. 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. IMP should be administered using the oral dosing syringe provided.

In order to maintain the blind across all dose groups, all subjects who do not continue into the open-extension study will participate in a dose-tapering procedure over the course of 8 days. On the first day of the tapering period subjects in the ZX008 0.8 mg/kg/day group will decrease to a dose of ZX008 0.4 mg/kg/day BID (maximum 30 mg/day). After 4 days at this dose level (Study Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group will decrease their dose to 0.2 mg/kg/day. Subjects in the ZX008 0.2 mg/kg/day group will decrease their dose to placebo on the first day of tapering while doses in the placebo group will remain constant throughout the tapering procedure. On Study Day 9, all subjects will stop taking study medication. The taper is expected to take a total of 8 days (Table 4). A new bottle of IMP will be started by the subject at each level of the taper step.

Table 4: Taper Algorithm

Randomized Group	Taper Step 1 Day 1-4 after study completion or early termination	Taper Step 2 Days 5-8 after study completion or early termination
ZX008 0.2 mg/kg/day	Placebo	Placebo
ZX008 0.8 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
Placebo	Placebo	Placebo
Note: maximum daily dose of ZX008 is 30 mg.		

5.5.5 Transition Period

Subjects who complete the Maintenance Period and will be continuing into the open-label extension study will be transitioned from double-blind study medication to open-label ZX008 (Table 5). 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 should be administered using the oral dosing syringe provided.

All subjects entering the open-label extension study will be transitioned from their blinded daily dose (placebo, 0.2 mg/kg/day, 0.8 mg/kg/day, or 30 mg/day) to the 0.2 mg/kg dose during the 2-week interval between Visits 12 and 13, without breaking the blind. The IVR/IWR system will assign two bottles of IMP to the subject, one for each step in the transition. 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 5: Transition Algorithm

Dose Group in Double-Blind	Transition Step 1 Day 1-4 after Visit 12	Transition Step 2 Days 5-14 after Visit 12
ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
Placebo	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
Note: maximum daily dose of ZX008 is 30 mg.		

Subjects who had been randomized to placebo increase their dose to 0.2 mg/kg/day beginning on day 1 of the transition (the day following Visit 12; Study Day 100.) Subjects who had been randomized to 0.2 mg/kg/day will continue to receive that dose. Subjects who had been randomized to 0.8 mg/kg/day or were receiving the maximum dose of 30 mg/day decrease to a dose of ZX008 0.4 mg/kg/day. After 4 days at this dose level (day 5; Study Day 104), these subjects will decrease their dose to 0.2 mg/kg/day. Subjects will report to the clinic on day 15 (Study Day 113) for enrollment into the open-label extension study.

5.6 BLINDING

At the end of the Baseline Period, subjects who qualify to enter the study will be randomized to receive ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day (maximum dose: 30 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 blinding scheme instituted for this study will ensure that the volume of study medication taken cannot be associated with the dose group, thus unblinding the study. This is achieved by random assignment of different concentrations of the ZX008 oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the IVR/IWR system. 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 and to the concentration of ZX008 oral solution. If an investigator feels the blind should be broken, he/she can do so when necessary for treatment decisions. However, the investigator should endeavor to discuss with the Medical Monitor or Sponsor's Medical Representative, if available. 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 the event. The subject will be discontinued from the clinical trial upon breaking of the blind and the decision whether the subject can enter the separate open-label extension study will rest with the Sponsor if the subject exited Study 1502 prior to completion.

5.7 PRIOR AND CONCOMITANT MEDICATION

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 medication 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 decrease in a concomitant AED 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 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 CRF.

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 CRF.

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 medication 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 Medication and Food

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 following concomitant medications are prohibited during the clinical trial:

- AEDs: Phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, retigabine/ezogabine
- Stiripentol (STP): Subjects must be off STP for a minimum of 21 days prior to the Screening visit.
- 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.
- Drugs that interact with central serotonin, including, but not limited to: imipramine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, vortioxetine
- Drugs that increase cardiovascular risk including: atomoxetine and those with noradrenergic reuptake properties (NRIs, SNRIs)
- Drugs intended to facilitate weight loss
- Other: any form of marijuana, THC and derivatives (including Epidiolex®)

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

Study procedures will be conducted according to the Schedule of Assessments in Table 1. Time windows for all assessments are detailed in Table 6.

Table 6: Time Windows for Assessments

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Clinic; Study Day -43 to -42 or -42 to -41):	Not applicable
Visit 2 (Phone; Study Day -21)	± 3 days
Visit 3 (Clinic; Study Day -1; Randomization)	+ 4 days[a]
Visits 4, 5 (Phone: Study Days 4, 8)	± 3 days
Visit 6 (Clinic; Study Day 15)	± 4 days
Visit 7 (Phone: Study Day 29)	± 4 days
Visit 8 (Clinic; Study Day 43)	± 4 days
Visit 9 (Phone: Study Day 57)	± 4 days
Visit 10 (Clinic; Study Day 71)	± 4 days
Visit 11 (Phone: Study Day 85)	± 4 days
Visit 12 (Clinic: Study Day 99)	± 4 days
Visit 13 (Clinic; Study Day 113; 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

a In cases where the screening period is extended beyond 42 days, the immediate 42 days before the Randomization visit will be used to calculate the baseline seizure frequency

6.1 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.

6.1.1 Screening, Clinic Visit 1 (Study Day -42)

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 (e.g., 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 PedsQL Family Impact, HADS, and 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
- Record prior medications
- Complete physical examination, including height, weight, and calculation of BMI
- Complete neurological examination
- 12-lead electrocardiogram
- Doppler ECHO (this may be obtained any time between Study Day -42 and Study Day -21)
- Vital signs
- 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
- 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 DS 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 re-screened 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.

6.1.2 Phone Visit 2 (Study Day -21)

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

- AEs
- AESI

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

6.1.3 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 pharmacokinetic 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
- 12-lead ECG
- Urine pregnancy test for females of child-bearing potential

- Laboratory evaluation (serum chemistry, and hematology, and urinalysis)
- Collect plasma sample for AED pharmacokinetic 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)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6)
- PedsQL Family Impact module (Appendix 6)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- Affective symptoms of parent/caregiver using the HADS scale (Appendix 8)
- Record AEs
- Record AESI
- When eligibility for the Titration Period is confirmed, randomize (blinded) subject to treatment assignment (ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day, 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 TITRATION AND MAINTENANCE PERIODS

6.2.1 Titration Period Study Day 1

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

6.2.2 Phone Visits 4 and 5 (Titration Period Study Days 4 and 8)

Site personnel will contact the subject via telephone on Titration Period Study Days 4 and 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.

6.2.3 Clinic Visit 6 (Titration Period Study Day 15)

Subjects will report to the clinic in the morning on Titration Period Study Day 15. 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
- Obtain vital signs
- 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 AED pharmacokinetic 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)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (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

6.2.4 Phone Visit 7 (Maintenance Period Study Day 29)

Site personnel will contact the subject via telephone on Maintenance Period Study Day 29 and record the following:

- AEs
- AESI
- Concomitant medications

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

6.2.5 Clinic Visit 8 (Maintenance Period Study Day 43)

Subjects will report to the clinic in the morning on Maintenance Period Study Day 43. 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 Study Day-1, the IMP dose will be recalculated)**
- Obtain vital signs
- 12-lead electrocardiogram
- Doppler ECHO (this must be obtained any time between Study Day 40 and Study 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 ZX008 pharmacokinetic evaluation at the following timepoints: within 1 hour prior to the morning dose of study medication, and 1, 2 and 4-6 hours after the morning dose of study medication
- Collect plasma sample for AED pharmacokinetic 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)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6)
- Affective symptoms of parent/caregiver using the HADS scale (Appendix 8)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (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

6.2.6 Phone Visit 9 (Maintenance Period Study Day 57)

Site personnel will contact the subject via telephone on Maintenance Period Study Day 57 and record the following:

- AEs
- AESI
- Concomitant medications

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

6.2.7 Clinic Visit 10 (Maintenance Period Study Day 71)

Subjects will report to the clinic on Maintenance Period Study Day 71. 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
- Obtain vital signs
- 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)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (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

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

6.2.8 Phone Visit 11 (Maintenance Period Study Day 85)

Site personnel will contact the subject via telephone on Maintenance Period Study Day 85 and record the following:

- AEs
- AESI
- Concomitant Medications

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

6.2.9 Clinic Visit 12 (Maintenance Period Study Day 99): End of Study/Early Termination

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 study if they have completed 12 weeks of treatment in the Maintenance Period. Other circumstances for participation in the extension study 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 study 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 study 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
- Obtain vital signs
- 12-lead electrocardiogram
- Doppler ECHO (must be performed any time between Study Day 90 and Study Day 113; if subject terminates 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 (see Table 7).
- 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 AED pharmacokinetic 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)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (assessed by investigator)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6)

- PedsQL Family Impact module (Appendix 6)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- Affective symptoms of parent/caregiver using the HADS scale (Appendix 8)
- Record AEs
- Record AESIs
- 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 study

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

6.3 POST-DOSE VISIT (CLINIC VISIT 13; STUDY DAY 113)

For subjects entering the open-label extension study, the subject will visit the clinic on Study Day 113. 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
- AESIs
- Concomitant medications
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

If the subject does not enter the open-label extension study (or discontinues from the study early), the subject will visit the clinic on Study Day 113 (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
- AESIs
- Concomitant medications
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

6.4 CARDIAC FOLLOW-UP VISIT (CLINIC VISIT 14; STUDY DAY 197-281)

If the subject completes the study but does not enter the open-label extension study 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 in Table 7. 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 than 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 7: Schedule of Post-Treatment Cardiac Follow-up

Parameter	Duration of Blinded[a] or Fenfluramine Treatment				
	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 and 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 and 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

[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.

6.5 ESTIMATED BLOOD VOLUME COLLECTION

The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately 99.7 mL, as outlined in Table 8.

Table 8: Estimated Blood Volume Collection*

Assessment	Baseline Period (study day)			Titration + Maintenance Period (study day)			
	Screening (Day -42 to -41)	Randomization Day -1	Day 15	Day 43	Day 71	Day 99	Total
Clinical Chemistry	4mL	4mL	4mL	4mL	4mL	4mL	24mL
LH, FSH, Estradiol, Testosterone, Prolactin		4mL		4mL	4mL	4mL	16mL
Genotyping	5 mL						5 mL
Hematology	2mL	2mL	2mL	2mL	2mL	2mL	12mL
IGF-1, GH		2.5mL		2.5mL	2.5mL	2.5mL	10 mL
Coagulation		2.7mL					2.7mL
Cannabidiol	2mL	2mL	2mL	2mL	2mL	2mL	12mL
ZX008 PK plasma				4 x 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	13mL	19.2mL	10mL	26.5mL	14.5mL	16.5mL	**99.7 mL**

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 43/Visit 8 the pharmacokinetic 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 9:

Table 9: 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

7. EFFICACY, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

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

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

7.1 EFFICACY ASSESSMENTS

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)

B: Focal With or Without Retained Awareness

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)

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 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 (e.g. 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

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.

The 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 document in the source file prior to rating.

7.1.3 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. 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).

7.1.4 PedsQL Quality of Life Inventory (PedsQL)

The PedsQL (Appendix 6) is a pediatric modular measure of health-related QoL completed by the parent/caregiver on behalf of the subject. It consists of 4 core scales that measure physical, emotional, social, and school functioning. The PedsQL will be conducted according to the schedule in Table 1.

7.1.5 Parent/Caregiver Quality of Life

The impact on the quality of life of the parent/caregiver responsible for a patient with DS will be assessed according to the schedule in Table 1 using 3 scales: the EQ-5D-5L, the HADS, 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 HADS (Appendix 8) is a tool commonly used to determine the levels of anxiety and depression that a person is experiencing. It is a 14-item scale that generates ordinal data. Seven of the items relate to anxiety and 7 relate to depression.

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. This module will not be used in Norway, Sweden, and Denmark.

The parent/caregiver will be asked to indicate the appropriate response that adequately describes how the care of their child with DS has impacted their quality of life using the scales described above.

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.

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. 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. 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.

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:

- 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), carbon dioxide (CO_2), chloride (Cl), creatinine, creatine kinase, gamma-glutamyl transferase (GGT), globulin, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), thyroid function (T3, T4, and thyroid stimulating hormone [TSH]),

total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid.

- 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
- Coagulation: Prothrombin time (PT)/International normalized ratio (INR), activated partial thromboplastin time (PTT)
- Whole blood cannabidiol
- 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 9).

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. 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.

7.2.7 Electrocardiograms

Twelve-lead ECGs will be conducted during study as outlined in Table 1 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 the investigator's overall interpretation will be recorded.

7.2.8 Doppler Echocardiography

Doppler echocardiography will be conducted at a facility with experience for the subject's age during study as outlined in Table 1. 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 9 (Adverse Events of Special Interest). A manual of proper ECHO technique for sites is provided in a separate document.

7.2.9 Tanner Staging

Tanner Staging (Appendix 5) will be assessed for subjects >7 years old during the study as outlined in Table 1. 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'.

7.2.10 Columbia-Suicide Severity Rating Scale

C-SSRS (Appendix 2) will be assessed during study as outlined in Table 1. 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.

7.2.11 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 9.

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.

7.2.12 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. 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).

7.3 PHARMACOKINETIC ASSESSMENTS

Blood samples for PK assessments of fenfluramine and its metabolite (norfenfluramine) will be obtained from all subjects via an indwelling cannula or by venipuncture.

Blood samples for PK assessment (2 mL) will be obtained at the following time points:

- Maintenance Period Study Day 43: 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.

7.4 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

A serious adverse event (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 status epilepticus (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 AESIs for the ZX008 program (Table 10).

Table 10: Adverse Events of Special Interest

CV/Respiratory
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.
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 a systolic pressure ≥140 mmHg after repeated measures during one visit. Blood pressure should be repeated at appropriate times within the visit.
5. Jugular venous distention- visible bulging of the external jugular veins on either side of the neck
6. New onset heart murmur
7. Pulmonary rales – an abnormal respiratory sound heard during auscultation of the lungs, which is also described as a crackle.
8. Tachycardia – a persistent HR >30% above the screening value and unrelated to exercise, exertion or anxiety. Heart rate should be repeated at appropriate times within the visit.
9. 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
10. Signs on ECHO indicative of potential valvulopathy □ 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
11. Signs on ECHO indicative of pulmonary hypertension a. Tricuspid Regurgitation Jet velocity > 2.8 msec 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 caval vein (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/sec vi. Tricuspid Anular Plane Systolic Excursion below 18 mm or below Z-score – 2

Table 10: Adverse Events of Special Interest (continued)

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 – serum blood glucose more than 20% below the glucose level on Study Day -1 value or more than 10% below LLN (reference range 60 – 140 mg/dL)
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

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, magnetic resonance imaging (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 11).

Table 11: 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.
CDISC SDTM 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), 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 medication) 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 study, 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 a 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 iHC 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.

Adverse events occurring in the period between the time the subject gave written informed consent and the first exposure to IMP that meet one or more of the seriousness criteria for AEs must be

reported to the sponsor and the Medical Monitor in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs 15 days after the last dose of study drug or the last visit, whichever is later that is considered to be causally related to IMP must be **reported immediately (i.e., within 24 hours of the investigator becoming aware of the event) to the sponsor and 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. In the event of a SAE a blood sample for ZX008 and AED PK should be collected as soon as feasible.

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.

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, triscuspid) will be reported to the investigator with grades of normal, trace, mild, moderate or severe. If the ECHO result has progressed in severity since the last reading then new oversight measures will be enacted as described below in Levels 1-3. Table 12 describes the severity of ECHO findings with the level of increasing oversight if the subject is to remain in the study.

Table 12: Clinical Measures Enacted Upon Increasing Severity of ECHO Findings

	Valve			
Severity	Aortic	Mitral	Pulmonary	Tricuspid

Normal	Level 1	Level 1	Level 1	Level 1
Trace	Level 2	Level 2	Level 1	Level 1
Mild	Level 2	Level 2	Level 1	Level 1
Moderate	Level 3	Level 3	Level 3	Level 3
Severe	Level 3	Level 3	Level 3	Level 3

Level 1: Continue per protocol

Level 2:

1. If there is a desire to continue study medication:
    a. The investigator will evaluate the efficacy to date based on study diaries and consult with the parent/guardian, and determine whether study treatment was associated with significant, meaningful benefit in number, severity and/or duration of seizures and/or on the impact on daily functioning.
    b. The investigator will consider whether the subject has had reasonable trials (dose and duration) of other available anticonvulsants (e.g. valproic acid, clobazam, or topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.
2. If the investigator feels consideration of continued treatment is warranted considering benefit and potential 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. IDMSC 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, valproic acid, clobazam, topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.

2. If the investigator feels consideration of continued treatment is warranted considering benefit and potential risks, and the parent/guardian feels strongly that the child be maintained on the study medication when understanding the risks, the parent/guardian must sign a new consent which describes the additional risks and the child should provide assent if possible.
    a. If both of these conditions are not met, the subject is discontinued from treatment.
3. 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 subjects 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 FDA 21 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

The results of the only randomized, placebo-controlled studies in subjects with Dravet syndrome can be found in the European Public Assessment Report (EPAR) for stiripentol (EMA, 2007). The EPAR summarizes the results from two studies: STICLO France and STICLO Italy. In the stiripentol groups, the 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 0.8 mg/kg/day 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. Similar assumptions and calculations yield a requirement for an additional 35 subjects in the 0.2 mg/kg/day ZX008 group. Thus, the total sample size is planned to be 105 subjects (35 per arm).

10.2 ANALYSIS POPULATIONS

10.2.1 Safety (SAF) Population

All safety analyses will be performed on the 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 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 ZDX008 0.8 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 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 will be randomly assigned to one of three treatment groups: ZX008 0.8 mg/kg/day, ZX008 0.2 mg/kg/day, or placebo.

10.4 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 first 14 days of treatment while subjects are titrated to their randomized dose. It begins on the first day of treatment (Study Day 1) and extends through Study Day 15 regardless of the exact day on which a subject reaches his or her assigned dose. 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. It begins on Study Day 16 and extends through Study Day 99.

Titration +Maintenance (T+M) Period

The T+M period combines the Titration and Maintenance periods, beginning on Study Day 1 and extending through Study Day 99. 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 to a final visit 2 weeks later; ie, from Study Day 99 through Study Day 113. Only subjects who do not roll over enrollment into the open-label extension will participate in the Follow-up Period.

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, standard deviations, 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.

Efficacy and PK data will be summarized by treatment (ZX008, placebo) age cohort (<6 years and ≥6 years of age), as well as for the total subjects in the population.

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

10.5.1 Efficacy Analyses

10.5.1.1 Primary Efficacy Analysis

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 (three levels) and age group (< 6 years, ≥6 years) as factors, and with baseline frequency as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day 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 test such as the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the van Elteren test will be used to assess the primary objective.

An additional analysis will be performed to assess the sensitivity of the primary analysis to changes in dose or type of concomitant AED medications that may occur during the course of the trial, which are protocol violations. Specifically, the primary analysis will be repeated with a factor added to indicate whether a subject had a change in prescribed dose or type of concomitant AED medication during the T+M period. Further exploratory analyses may be conducted if changes in concomitant AED medication appear to have a significant impact on the primary outcome.

Additional analyses will compare the 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

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 0.8 mg/kg/day 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 0.8 mg/kg/day and placebo groups will be compared using a log-rank test.

The MCSF in the ZX008 0.2 mg/kg/day group will be compared to the placebo group using the same methods employed for the primary analysis. Analyses of other key secondary endpoints involving the ZX008 0.2 mg/kg/day group will employ similar methods as those used to compare ZX008 0.8 mg/kg/day to placebo. Whenever feasible, secondary analyses involving either ZX008 0.8 mg/kg/day or ZX008 0.2 mg/kg/day 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

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 beginning with comparisons of ZX008 0.8 mg/kg/day to placebo 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 evaluation of key secondary endpoints continues by comparing the ZX008 0.2 mg/kg/day group to placebo in the following order:

- 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.

10.5.2 Safety Analyses

Summaries of safety data will be presented by treatment – ZX008 0.8 mg/kg/day, ZX008 0.2 mg/kg/day 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 serious AEs (SAEs). Selected summaries will be repeated broken out by age group, ie, for ages <6 years and ≥6 years.

Hematology and chemistry laboratory results 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. 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 echocardiogram, C-SSRS, Tanner Staging results, etc, will be summarized appropriately, by treatment. All safety summaries will be based on the SAF Population.

10.5.3 Pharmacokinetic Analyses

All data will be evaluated using population PK analysis methods and the methods will be described in detail in a separate PK analysis plan. In brief, the plan is to use published data to construct a population PK model for fenfluramine in adults. Given the age range of subjects to be enrolled in this study, it will be possible to use the known ontogeny of drug disposition in children to predict fenfluramine PK in subjects with Dravet syndrome from the population PK model. The robustness of the empirical model will then be confirmed by applying the model to PK data collected from this study. In this way, the effect of body size, age, and any other relevant factors can be quantified to assure that an adequate understanding of fenfluramine PK is obtained.

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: the population mean and interindividual variability estimates from the fit of the population PK model; summary statistics of the plasma concentrations by PK sampling time and of the individual, derived plasma PK parameters (Cmax, AUC_{0-t}, T_{max}, and $t_{1/2}$) by treatment group. The clinical study report will also contain a comparison of the PK of fenfluramine in the children enrolled in this study to historical data from adults.

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 IDMC 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 IDMC 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 IDMC 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/or 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 [HIPAA]), 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

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
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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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 areolae.

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

VDH 1059

APPENDIX 6 – PEDsQL (INCLUDING FAMILY IMPACT MODULE)

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 ❑

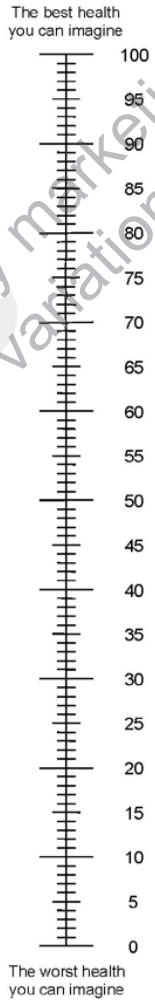
ANXIETY / DEPRESSION

- 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 = ☐



3

APPENDIX 8 – HOSPITAL ANXIETY AND DEPRESSION SCALE

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 – PROTOCOL AMENDMENT 1

Summary of Changes

Clarifications and changes were made to the protocol and include the following:

- Sponsor name change
- Removed the following clinical laboratory tests at Visits 1 and 6: LH, FSH, estradiol, testosterone, GH, prolactin, and IGF-1
- Clarified the maximum dose of ZX008 is 30 mg/day
- Clarified the collection duration of prior and concomitant AEDs
- Clarified data to be collected with the use of rescue medication
- Added new section of collection of data for AEs requiring hospitalization
- Replaced CHU9D with PedsQL
- Updated statistical analysis section to be consistent with the separate statistical analysis plan
- Clarified study duration for participants
- Clarified inclusion criterion #7 regarding the requirement for a whole blood sample for a broad epilepsy-related gene panel
- Added requirement that subjects who may qualify for and plan to enroll into the separate open-label extension study at the end of this study should be consented prior to Visit 12
- Clarified for all questionnaires and rating scales when rater substitution is acceptable for the clinic staff and the parent/caregiver

Clarifications and changes were made based on feedback received from the United States Food and Drug Administration, and include the following:

- Clarified randomization inclusion criteria, post-treatment cardiac follow-up, and AESI with regard to valve regurgitation seen on ECHO.
- Clarified that the central cardiac reader will provide consultation to the IDSMC when a subject may be removed from the study due to development of signs or symptoms indicative of valvulopathy, regurgitation, or pulmonary hypertension
- Clarified expedited reporting of cardiac events other than SAEs
- Added section on grading of and follow-up for ECHO findings
- Added the assessment of cognition for subjects ≥5 years of age, so that all study participants are now being assessed for cognition using the BRIEF. The description of the BRIEF was moved from the efficacy section to the safety section.

Clarifications and changes were made based on feedback received from the European Voluntary Harmonization Procedure Clinical Trials Group, and include the following:

- Updated contraception requirements for the study

- Clarified when subjects must be discontinued from the study

Clarified that the investigator may discontinue a subject from the study in the case of a medical emergency

- Added statistical information regarding sensitivity analyses for concomitant AED medication changes during the study

The rationale for each change/clarification also is provided below.

List of Specific Changes

Additions are marked in **bold** and deletions are marked in ~~strikethrough~~. Minor editorial changes, such as the correction of typing or formatting errors, updating headers and footers, tables of contents, and list of references, etc, are not listed.

Rationale: There has been a name change for the sponsor's subsidiary.	
Original Text	**Amendment Text**
Title page, Signature of Sponsor page, Synopsis, Table 2, and document headers Brabant Pharma Limited	Title page, Signature of Sponsor page, Synopsis, Table 2, and document headers ~~Brabant Pharma Limited~~ **Zogenix International Limited**
Rationale: To replace the CHU9D with the PedsQL for the assessment of quality of life.	
Original Text	**Amendment Text**
Synopsis, Section 2.3 Additional secondary efficacy objectives of the study are: • To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints: o The change from baseline in the Child Health Utility 9D Scale (CHU9D) score. Synopsis (Criteria for Evaluation/Efficacy), Section 2.7.1 • CHU9D to measure changes in quality of life of the subject Table 1 was updated and is not presented here. Sections 6.1.3, 6.2.5, 6.2.9, and 7.1.4 The following procedures will be performed: • CHU9D (Appendix 6) Appendix 6 was updated and is not presented here. Section 7.1.5 The impact on the quality of life of the parent/caregiver responsible for a patient with DS will be assessed according to the schedule in Table 1 using	Synopsis, Section 2.3 Additional secondary efficacy objectives of the study are: • To demonstrate that the ZX008 0.2 and 0.8 mg/kg/day dose groups are (independently) superior to placebo on the following endpoints: o The change from baseline in the ~~Child Health Utility 9D Scale (CHU9D)~~ **PedsQL** score. Synopsis (Criteria for Evaluation/Efficacy), Section 2.7.1 • ~~CHU9D~~ **PedsQL** to measure changes in quality of life of the subject Table 1 was updated and is not presented here. Sections 6.1.3, 6.2.5, 6.2.9, and 7.1.4 The following procedures will be performed: • ~~CHU9D~~ **Peds QL** (Appendix 6) Appendix 6 was updated and is not presented here. Section 7.1.5 The impact on the quality of life of the parent/caregiver responsible for a patient with DS will be assessed according to the schedule in Table 1 using ~~2~~ 3 scales:

2 scales: the EQ-5D-5L and the HADS. 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**,** ~~and~~ the HADS**, 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 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. This module will not be used in Norway, Sweden, and Denmark.**
Rationale: To update the statistical sections of the protocol to be consistent with the separate statistical analysis plan.	
Original Text	**Amendment Text**
Synopsis, Section 3.1, Section 5.5.1 *Synopsis-Methodology* Randomization will be stratified by age group (< 6 years, ≥6 to 18 years) to ensure balance across treatment arms, and at least 40% of subjects will be in each age group. Synopsis *Synopsis-Statistical Methods/Efficacy* Primary Efficacy Analysis: 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 (three levels) and age group (< 6 years, ≥6 to 18 years) as factors, and with Baseline MCSF as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day group to the placebo group using a two-sided test at the alpha=0.05 level of significance. Since the ANCOVA used in the primary analysis relies on assumptions of normality, the primary endpoint also will be analyzed using a nonparametric method that does not require as stringent assumptions. Specifically, the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the	Synopsis, Section 3.1, Section 5.5.1 *Synopsis-Methodology* Randomization will be stratified by age group (< 6 years, ≥6 ~~to 18~~ years) to ensure balance across treatment arms, and at least 40% of subjects will be in each age group. Synopsis *Synopsis-Statistical Methods/Efficacy* Primary Efficacy Analysis: 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 (three levels) and age group (< 6 years, ≥6 ~~to 18~~ years) as factors, and with Baseline MCSF as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day 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**

van Elteren test will be used to assess the primary objective.	**a change in concomitant AED medication during the T+M period.** ~~Since the ANCOVA used in the primary analysis relies on assumptions of normality, the primary endpoint also will be analyzed using a nonparametric method that does not require as stringent assumptions. Specifically, the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the van Elteren test will be used to assess the primary objective.~~
Section 10.5.1.1 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 (three levels) and age group (< 6 years, ≥6 to 18 years) as factors, and with baseline frequency as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day 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. Specifically, the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the van Elteren 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.	Section 10.5.1.1 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 (three levels) and age group (< 6 years, ≥6 ~~to 18~~ years) as factors, and with baseline frequency as a covariate. The primary analysis will compare the ZX008 0.8 mg/kg/day 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. ~~Specifically,~~ **A test such as** the van Elteren test, which extends the Wilcoxon rank sum test to include stratified data, will be used to compare the ZX008 0.8 mg/kg/day group to the placebo group while stratifying for age group. If normality assumptions are not met, the results of the van Elteren test will be used to assess the primary objective. **An additional analysis will be performed to assess the sensitivity of the primary analysis to changes in dose or type of concomitant AED medications that may occur during the course of the trial, which are protocol violations. Specifically, the primary analysis will be repeated with a factor added to indicate whether a subject had a change in prescribed dose or type of concomitant AED medication during the T+M period. Further exploratory analyses may be conducted if changes in concomitant AED medication appear to have a significant impact on**

	the primary outcome. 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.
Section 10.5.1.2 The longest interval between convulsive seizures will be calculated for each subject over the entire T+M period. Subjects whose longest interval extends to the end of treatment or end of study will be considered right-censored. The ZX008 0.8 mg/kg/day and placebo groups will be compared using a log-rank test. The median length of the longest seizure-free interval will be presented for each treatment group.	Section 10.5.1.2 The longest interval between convulsive seizures will be calculated for each subject over the entire T+M period. ~~Subjects whose longest interval extends to the end of treatment or end of study will be considered right-censored.~~ The ZX008 0.8 mg/kg/day and placebo groups will be compared using a log-rank test. ~~The median length of the longest seizure-free interval will be presented for each treatment group.~~
Section 10.5.1.3 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. If any test fails to achieve significance at the α=0.05 level, then no test lower in the hierarchy can achieve statistical significance.	Section 10.5.1.3 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. ~~If any test fails to achieve significance at the α=0.05 level, then no test lower in the hierarchy can achieve statistical significance.~~
Section 10.5.2 Selected summaries will be repeated broken out by age group, ie, for ages <6 years and ≥6 to 18 years.	Section 10.5.2 Selected summaries will be repeated broken out by age group, ie, for ages <6 years and ≥6 ~~to 18~~ years.
Rationale: To clarify inclusion criterion #7 regarding the requirement for a whole blood sample for a broad epilepsy-related gene panel.	
Original Text	**Amendment Text**
Synopsis, Section 4.1 Subject agrees to provide whole blood sample for a Dravet syndrome genetic testing panel, if genetic screening results from an acceptable commercial laboratory or medical center are not available for SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, GABRD, GABRG2, and PCDH19.	Synopsis, Section 4.1 Subject agrees to provide whole blood sample for a **broad epilepsy-related gene testing panel** ~~Dravet syndrome genetic testing panel, if genetic screening results from an acceptable commercial laboratory or medical center are not available for SCN1A, SCN1B, SCN2A, SCN8A, SCN9A, GABRD, GABRG2, and PCDH19~~.
Rationale: To clarify the study duration for participants.	
Original Text	**Amendment Text**
Synopsis Duration of Treatment: All subjects will receive ZX008 or matching placebo for up to approximately 14 weeks (Titration Period=2 weeks; Maintenance Period=12 weeks). After completion of the	Synopsis Duration of Treatment: All subjects will receive ZX008 or matching placebo for up to approximately ~~14~~ **16** weeks (Titration Period=2 weeks; Maintenance Period=12 weeks**; Taper/Transition=2 weeks**). After

Maintenance Period, eligible subjects may enroll in the open-label extension study.	completion of the Maintenance Period, eligible subjects may enroll in the open-label extension study**, after completion of the transition**.
Rationale: To add the requirement that subjects who may qualify for and plan to enroll into the separate open-label extension study at the end of this study be consented prior to Visit 12.	
Original Text	**Amendment Text**
Section 6.2.7 None Section 6.2.9 None	Section 6.2.7 **At Clinic Visit 10, compliant subjects who have tolerated IMP should be presented with the ICF for the open-label extension study. Informed consent for the open-label extension study must be signed at Visit 12 or earlier in order to enter the open-label extension study.** Section 6.2.9 **Informed consent for the open-label extension study must be signed at Visit 12 (if not signed earlier) in order to enter the open-label extension study.**
Rationale: To clarify for all questionnaires and rating scales when rater substitution is acceptable for the clinic staff and the parent/caregiver.	
Original Text	**Amendment Text**
Section 7.1 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. If that evaluator 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.	Section 7.1 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.** ~~If that evaluator 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.~~
Rationale: To add the assessment of cognition for subjects ≥5 years of age, so that all study participants are now being assessed for cognition using the BRIEF, and to move the description of the BRIEF from the efficacy section to the safety section.	
Original Text	**Amendment Text**
Synopsis, Section 2.4 The safety objective of the study is: o To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day to placebo with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate,	Synopsis, Section 2.4 The safety objective of the study is: o To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day to placebo with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate, temperature, and

temperature, and respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), and body weight. Cognitive Function will be assessed in subjects 5 years and older using the cognition domain score on the QOLCE. Cognitive function in subjects <5 years at baseline will be assessed using the Brief Rating Inventory of Executive Function-Preschool version (BRIEF-P).	respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), and body weight. Cognitive Function will be assessed ~~in subjects 5 years and older using the cognition domain score on the QOLCE. Cognitive function in subjects <5 years at baseline will be assessed~~ using **age-appropriate versions of** the Brief Rating Inventory of Executive Function ~~Preschool version~~ (BRIEF~~-P~~).
Synopsis (Criteria for Evaluation/Safety) • The cognition domain of the QOLCE will also be used to track cognitive function relative to baseline in children 5 years and older. The BRIEF-P will be administered to children younger than 5 years to track cognitive function.	Synopsis (Criteria for Evaluation/Safety), Section 2.7.2 • ~~The cognition domain of the QOLCE will also be used to track cognitive function relative to baseline in children 5 years and older.~~ The BRIEF will be administered to ~~children younger than 5 years to~~ track cognitive function.
Table 1 was updated and is not presented here.	Table 1 was updated and is not presented here.
Section 2.7.2 The safety endpoints of the study are: • Behavior Rating Inventory of Executive Function, Preschool Version (BRIEF-P) to measure cognition in subjects aged 2 to < 5 years at baseline	Section 2.7.2 The safety endpoints of the study are: • ~~Behavior Rating Inventory of Executive Function, Preschool Version (~~BRIEF~~-P)~~ to measure cognition ~~in subjects aged 2 to < 5 years at baseline~~
Sections 6.1.3, 6.2.5, and 6.2.9, The following procedures will be performed: • BRIEF-P for subjects < 5 years (Appendix 3)	Sections 6.1.3, 6.2.5, and 6.2.9 The following procedures will be performed: • BRIEF~~-P for subjects < 5 years~~ (Appendix 3)
Section 7.1.4 The BRIEF-P is a standardized, validated rating scale to measure executive function in preschool aged children within the home and school environments that will be assessed according to the schedule in Table 1. The BRIEF-P measures multiple aspects of executive functioning; scales include Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize.	Section 7.2.12 The BRIEF~~-P~~ is a standardized, validated rating scale to measure executive function in ~~preschool aged~~ children **ages 2-18 years** within the home and school environments; ~~that~~ **it** will be assessed according to the schedule in Table 1. The BRIEF~~-P~~ 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).**
Appendix 3 was updated and is not presented here.	Appendix 3 was updated and is not presented here.

Rationale: To update contraception requirements for the study.

Original Text	Amendment Text
Section 4.4 Subjects who are sexually active must use, with their partner, 2 approved methods of highly effective contraception from the time of informed consent until 90 days after the last dose of study medication. Two or more of the following methods are acceptable and must include at least 1 barrier method: • Surgical sterilization (ie, bilateral tubal ligation/salpingectomy, hysterectomy for female subjects or partners; vasectomy for male subjects or partners) • Placement of an intrauterine device or intrauterine system • Hormonal contraception (implantable, patch, oral, injectable) • Barrier methods (for male subjects, this must be a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps]; for female subjects, either their partner's use of a condom or the subject's use of an occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) Male subjects who have been sterilized or have partners of non-childbearing potential (including homosexual men) are required to use one barrier method of contraception (condom). This is to prevent unintended exposure of the partner to the study drug via seminal fluid. Male subjects who have pregnant partners are required to use one barrier method of contraception (condom). 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, must comply with the contraceptive requirements detailed above. Female subjects of non-childbearing potential, ie, women who are post-menopausal (defined as spontaneous amenorrhea for at least 1 year without another cause or spontaneous amenorrhea for at least 6 months confirmed by a follicle stimulating hormone [FSH] result of ≥40 IU/mL), or permanently sterilized	Section 4.4 ~~Subjects who are sexually active must use, with their partner, 2 approved methods of highly effective contraception from the time of informed consent until 90 days after the last dose of study medication.~~ ~~Two or more of the following methods are acceptable and must include at least 1 barrier method:~~ ~~• Surgical sterilization (ie, bilateral tubal ligation/salpingectomy, hysterectomy for female subjects or partners; vasectomy for male subjects or partners)~~ ~~• Placement of an intrauterine device or intrauterine system~~ ~~• Hormonal contraception (implantable, patch, oral, injectable)~~ ~~• Barrier methods (for male subjects, this must be a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps]; for female subjects, either their partner's use of a condom or the subject's use of an occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository)~~ ~~Male subjects who have been sterilized or have partners of non-childbearing potential (including homosexual men) are required to use one barrier method of contraception (condom). This is to prevent unintended exposure of the partner to the study drug via seminal fluid.~~ ~~Male subjects who have pregnant partners are required to use one barrier method of contraception (condom).~~ ~~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, must comply with the contraceptive requirements detailed above.~~ ~~Female subjects of non-childbearing potential, ie, women who are post-menopausal (defined as spontaneous amenorrhea for at least 1 year without another cause or spontaneous amenorrhea for at least 6 months confirmed by a follicle stimulating hormone [FSH] result of ≥40 IU/mL), or permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral~~

(eg, tubal occlusion, hysterectomy, bilateral salpingectomy, as determined by subject medical history), are not required to use any contraception during this study.	~~salpingectomy, as determined by subject medical history), are not required to use any contraception during this study.~~ **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 effective contraception from the time of informed consent until 90 days after study discharge.** **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 30 days following the last follow up visit.** **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)**
	
	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.

Rationale: To clarify when subjects must be discontinued from the study.	
Original Text	**Amendment Text**
Section 4.5 Subjects may be discontinued from the study for the following reasons, if deemed appropriate by the sponsor or investigator: *(list of reasons is unchanged).*	Section 4.5 Subjects ~~may~~ **must** be discontinued from the study for the following reasons, if deemed appropriate by the sponsor or investigator: *(list of reasons is unchanged).*
Rationale: To clarify that the investigator may discontinue a subject from the study in the case of a medical emergency.	
Original Text	**Amendment Text**
Section 5.6 The blinding scheme instituted for this study will ensure that the volume of study medication taken cannot be associated with the dose group, thus unblinding the study. This is achieved by random assignment of different concentrations of the ZX008 oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the IVR/IWR system. 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 and to the concentration of ZX008 oral solution. The Medical Monitor will have the ability to unblind subjects in the case of an emergency.	Section 5.6 The blinding scheme instituted for this study will ensure that the volume of study medication taken cannot be associated with the dose group, thus unblinding the study. This is achieved by random assignment of different concentrations of the ZX008 oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the IVR/IWR system. 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 and to the concentration of ZX008 oral solution. ~~The Medical Monitor will have the ability to unblind subjects in the case of an emergency.~~ **If an investigator feels the blind should be broken, he/she can do so when necessary for treatment decisions. However, the investigator should endeavor to discuss with the Medical Monitor or Sponsor's Medical Representative, if available. 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 the event. The subject will be discontinued from the clinical trial upon breaking of the blind and the decision whether the subject can enter the separate open-label extension study will rest with the Sponsor if the subject exited Study 1502 prior to completion.
Rationale: To remove the following clinical laboratory tests at Visits 1 and 6: LH, FSH, estradiol, testosterone, GH, prolactin, and IGF-1.	
Original Text	**Amendment Text**
Section 1.6 The approximate volume of blood (108.7 mL) planned for collection from each subject over the course of the entire study (Screening to End of Study, but not including repeat or additional tests ordered by the investigator) presents no undue risk to the subjects. Section 6.5 The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately 115.7 mL.	Section 1.6 The approximate volume of blood (~~115.7~~ **108.7** mL) planned for collection from each subject over the course of the entire study (Screening to End of Study, but not including repeat or additional tests ordered by the investigator) presents no undue risk to the subjects. Section 6.5 The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately ~~115.7~~ **108.7** mL.

Original Text

Table 8. Estimated Blood Volume Collection

Assessment	Baseline Period (study day)		Titration + Maintenance Period (study day)				
	Screening (Day -42 to -41)	Randomization Day -1	Day 15	Day 43	Day 71	Day 99	Total
Clinical chemistry	7.5 mL	7.5 mL	7.5 mL	7.5 mL	7.5 mL	7.5 mL	45 mL
LH, FSH, estradiol, testosterone, GH, prolactin	Included in Chemistry	Included in Chemistry	Included in Chemistry	Included in Chemistry	Included in Chemistry	Included in Chemistry	
Hematology	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	12 mL
Genotyping	5 mL	--	--	--	--	--	5 mL
IGF-1	3.5 mL	3.5 mL	3.5 mL	3.5 mL	3.5mL	3.5 mL	21 mL
Coagulation	--	2.7 mL	--	--	--	--	2.7 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 × 0.5 mL	--	--	2 mL
Approximate total blood volume per subject	20.0 mL	19.7 mL	17.0 mL	27.0 mL	15.0 mL	17.0 mL	115.7 mL

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

Amendment Text

Table 8. Estimated Blood Volume Collection

Assessment	Baseline Period (study day)		Titration + Maintenance Period (study day)				
	Screening (Day -42 to -41)	Randomization Day -1	Day 15	Day 43	Day 71	Day 99	Total
Clinical chemistry	7.5 mL	7.5 mL	7.5 mL	7.5 mL	7.5 mL	7.5 mL	45 mL
LH, FSH, estradiol, testosterone, GH, prolactin	~~Included in Chemistry --~~	Included in Chemistry	~~Included in Chemistry --~~	Included in Chemistry	Included in Chemistry	Included in Chemistry	
Hematology	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	12 mL
Genotyping	5 mL	--	--	--	--	--	5 mL
IGF-1	~~3.5 mL --~~	3.5 mL	~~3.5 mL --~~	3.5 mL	3.5mL	3.5 mL	~~21~~ **14** mL
Coagulation	--	2.7 mL	--	--	--	--	2.7 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 × 0.5 mL	--	--	2 mL
Approximate total blood volume per subject	~~20.0~~ **16.5** mL	19.7 mL	~~17.0~~ **13.5** mL	27.0 mL	15.0 mL	17.0 mL	~~115.7~~ **108.7 mL**

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

Rationale: To clarify the maximum dose of ZX008 is 30 mg/day.	
Original Text	**Amendment Text**
Section 5.5.2 After 4 days at this dose level (Study Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group will increase their dose to 0.4 mg/kg/day while doses in the other two groups will remain constant. On Study Day 9, the dose for the 0.8 mg/kg/day group will increase to the target dose. Table 3 None Section 5.5.4 On the first day of the tapering period subjects in the ZX008 0.8 mg/kg/day group will decrease to a dose of ZX008 0.4 mg/kg/day BID. Table 4 and Table 5 None	Section 5.5.2 After 4 days at this dose level (Study Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group will increase their dose to 0.4 mg/kg/day **(maximum 30 mg/day)** while doses in the other two groups will remain constant. On Study Day 9, the dose for the 0.8 mg/kg/day group will increase to the target dose **or a maximum of 30 mg/day.** Table 3 **Note: maximum daily dose of ZX008 is 30 mg.** Section 5.5.4 On the first day of the tapering period subjects in the ZX008 0.8 mg/kg/day group will decrease to a dose of ZX008 0.4 mg/kg/day BID (**maximum 30 mg/day)**. Table 4 and Table 5 **Note: maximum daily dose of ZX008 is 30 mg.**
Rationale: To clarify the collection duration of prior and concomitant AEDs.	
Original Text	**Amendment Text**
Section 5.7 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, antiepileptic drugs [AEDs], antibiotics) taken within 30 days prior to the Screening visit should also be captured.	Section 5.7 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, ~~antiepileptic drugs [AEDs]~~, 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**.
Rationale: To clarify data to be collected with the use of rescue medication.	
Original Text	**Amendment Text**
Section 5.7.3 Use of rescue medication is permitted during the study and should be recorded on the eCRF (day, time, medication[s], dose[s]) and in the diary (day, time). Repeated administrations within the same episode should be recorded separately.	Section 5.7.3 Use of rescue medication is permitted during the study and should be recorded on the eCRF (day, ~~time,~~ medication[s], dose[s]) and in the diary (day, time**frame associated with seizure episodes**). Repeated administrations within the same episode should be recorded separately.

Rationale: To add new section of collection of data for AEs requiring hospitalization.	
Original Text	**Amendment Text**
None	**Section 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, magnetic resonance imaging (MRI), x-ray, computed tomography CT) scan, surgery, and lumbar puncture/spinal tap.**
Rationale: To clarify randomization inclusion criteria, post-treatment cardiac follow-up, and AESI with regard to valve regurgitation seen on ECHO.	
Original Text	**Amendment Text**
Synopsis, Section 4.3, Section 6.4, Section 8.1.3 Synopsis and Section 4.3 Randomization Inclusion Criteria: 2. Subject does not have a cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination, including but not limited to any mitral, aortic, tricuspid or pulmonary valve regurgitation or signs of pulmonary hypertension, and is approved for entry by the cardiac central reader. Section 6.4, Table 6, footnote b Positive sign or symptom includes any sign of valve thickening or regurgitation (mitral, aortic, pulmonary, tricuspid), or sign or symptom indicative of potential pulmonary hypertension as adjudicated by the IPCAB. Section 8.1.3, Table 8 10. Signs on ECHO indicative of potential valvulopathy • ≥ mild valve regurgitation (aortic, mitral, tricuspid, or pulmonary) • Mean Mitral valve gradient ≥ 4 mmHg • Mean Aortic valve gradient ≥ 15 mmHg • Mean Tricuspid valve gradient > 4 mmHg • Mean Pulmonary valve gradient > 21 mmHg	Synopsis, Section 4.3, Section 6.4, Section 8.1.3 Synopsis and Section 4.3 Randomization Inclusion Criteria**:** 2. Subject does not have a cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination, including but not limited to ~~any~~ **trace** mitral, **or** aortic~~, tricuspid or pulmonary~~ valve regurgitation or signs of pulmonary hypertension, and is approved for entry by the ~~cardiac~~ central cardiac reader. Section 6.4, Table 7 footnote b Positive sign or symptom includes any ~~sign~~ **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. Section 8.1.3, Table 9 10. Signs on ECHO indicative of potential valvulopathy • **valve regurgitation (aortic or mitral)** • ≥ mild valve regurgitation (~~aortic, mitral,~~ tricuspid, or pulmonary) • Mean Mitral valve gradient ≥ 4 mmHg • Mean Aortic valve gradient ≥ 15 mmHg • Mean Tricuspid valve gradient ~~>~~ ≥ 4 mmHg • Mean Pulmonary valve gradient ~~>~~ ≥ 21 mmHg

Normal Values for Children 2-18 years • No regurgitation • Mean Mitral valve gradient < 4 mmHg • Mean Aortic valve gradient < 15 mmHg • Mean Tricuspid valve gradient ≤4mmHg • Mean Pulmonary valve gradient < 21mmHg	~~Normal Values for Children 2-18 years~~ ~~• No regurgitation~~ ~~• Mean Mitral valve gradient < 4 mmHg~~ ~~• Mean Aortic valve gradient < 15 mmHg~~ ~~• Mean Tricuspid valve gradient ≤4mmHg~~ ~~• Mean Pulmonary valve gradient < 21mmHg~~
Rationale: To clarify that the central cardiac reader will provide consultation to the IDSMC when a subject may be removed from the study due to development of signs or symptoms indicative of valvulopathy, regurgitation, or pulmonary hypertension.	
Original Text	**Amendment Text**
Section 4.5 Subjects may 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 and the investigator believe the benefit of continued participation does not outweigh the risk.	Section 4.5 Subjects may 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.
Rationale: To clarify expedited reporting of cardiac events other than SAEs.	
Original Text	**Amendment Text**
Section 8.8 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	Section 8.8 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**

Rationale: To add a new section on grading of, and follow-up for, ECHO findings.

Original Text	Amendment Text
None	**Section 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, triscuspid) 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 11 describes the severity of ECHO findings with the level of increasing oversight if the subject is to remain in the study.** **Table 11. Clinical Measures Enacted Upon Increasing Severity of ECHO Findings**

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

Level 1: Continue per protocol
Level 2:

1. **If there is a desire to continue study medication:**
    a. **The investigator will evaluate the efficacy to date based on study diaries and consult with the parent/guardian, and determine whether study treatment was associated with significant, meaningful benefit in number, severity and/or duration of seizures and/or on the impact on daily functioning.**
    b. **The investigator will consider whether the subject has had reasonable trials (dose and duration) of other available anticonvulsants (e.g. valproic acid, clobazam, or topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.**
2. **If the investigator feels consideration of**

	continued treatment is warranted considering benefit and potential 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 IDMSC.** **5. IDMSC 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 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 risk 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, valproic acid, clobazam, topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication. **2. If the investigator feels consideration of continued treatment is warranted considering the benefit and potential risk, and the parent/guardian feels strongly that the child be maintained on the study medication when understanding the risks, the parent/guardian must sign a new consent, which describes the additional risk and the child should provide assent if 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 risk and proposed monitoring plan if applicable for submission to the IDMSC.** **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**

APPENDIX 11 – PROTOCOL AMENDMENT 2

Summary of Changes

Clarifications and changes were made to the protocol and include the following:

- Removed atonic seizures and added tonic-atonic from the types of convulsive seizures in Inclusion Criterion #5.
- Removal of Inclusion Criterion #7 to clarify that participation in the epilepsy-related genetic testing is not required for participation.
- Updated the preclinical data information and, based on this information, revised the list of prohibited concomitant medications.
- Clarified that the number of convulsive seizures during the 6-week baseline period is ≥ 6.
- Added PedsQL Family Impact module to the efficacy measures.
- Clarify study days of Screening during the Baseline Period and the timing of assessments in that period.
- Collection of blood sample for epilepsy genotype panel is mandatory but not required at screening.
- Added the list of countries in which Diacomit® (stiripentol) is approved.
- Added supporting references to existing citations of data.
- Clarified the safety objective.
- Specify that the number of study centers is approximate.
- Clarified the duration of use of contraception after the last dose of study drug.
- Removal of social media policy from the reason or removing a subject from therapy or assessment.

The rationale for each change/clarification also is provided below.

List of Specific Changes

Additions are marked in **bold** and deletions are marked in ~~strikethrough~~. Minor editorial changes, such as the correction of typing or formatting errors, updating headers and footers, tables of contents, and list of references, etc, are not listed.

Rationale: To clarify the types of seizures that satisfy the requirement for the 12 weeks before screening.	
Original Text	**Amendment Text**
Inclusion Criterion, Synopsis and Section 4.1 Subject must have had ≥4 convulsive seizures (tonic-clonic, tonic, atonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.	Inclusion Criterion, Synopsis and Section 4.1 Subject must have had ≥4 convulsive seizures (tonic-clonic, tonic, **tonic-atonic**, ~~atonic,~~ clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.
Rationale: Remove the requirement for participation in epilepsy-related gene testing from the inclusion criteria.	
Original Text	**Amendment Text**

Inclusion Criterion 7, Synopsis and Section 4.1 Subject agrees to provide whole blood sample for a broad epilepsy-related gene testing panel.	Inclusion Criterion 7, Synopsis and Section 4.1 ~~Subject agrees to provide whole blood sample for a broad epilepsy-related gene testing panel.~~
Rationale: Revised the list of prohibited concomitant medications.	
Original Text	**Amendment Text**
Exclusion Criterion 8, Synopsis and Section 4.2 Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine- oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; cyproheptadine, and/or cytochrome P450 (CYP) 2D6/3A4/2B6 inhibitors/substrates (see Appendix 1). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)	Exclusion Criterion 8, Synopsis and Section 4.2 Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; **or** cyproheptadine, ~~and/or cytochrome P450 (CYP) 2D6/3A4/2B6 inhibitors/substrates~~ (see Appendix 1). (Note: Short- term medication requirements will be handled on a per case basis by the Medical Monitor.)
Rationale: Clarified that the number of convulsive seizures during the 6-week baseline period is ≥ 6.	
Original Text	**Amendment Text**
Randomization Inclusion Criterion 3, Synopsis and Section 4.3 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. Section 6.1.3 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.	Randomization Inclusion Criterion 3, Synopsis and Section 4.3 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. Section 6.1.3 This period is intended to ensure that subjects meet the study entry criteria and confirm they have experienced ≥6 ~~>6~~ convulsive seizures during the 6-week Baseline Period, with at least 2 seizures in each 3-week half of the Baseline Period.
Rationale: Added PedsQL Family Impact module to the efficacy measures.	
Original Text	**Amendment Text**
Synopsis, Criteria for Evaluation: Efficacy Not applicable Section 2.3, Additional Secondary Objectives Not applicable Section 2.7.1, Efficacy Endpoints Not applicable Section 6.1.3, 6.2.9 Not applicable	Synopsis, Criteria for Evaluation: Efficacy **PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver** Section 2.3, Additional Secondary Objectives **The change from baseline in the PedsQL Family Impact module score.** Section 2.7.1, Efficacy Endpoints **PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver** Section 6.1.3, 6.2.9 **PedsQL Family Impact module (Appendix 6)**

Rationale: Clarify study days of Screening during the Baseline Period.

Original Text	**Amendment Text**
Table 1: Schedule of Assessments 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. Table 6: Time Windows for Assessments Visit 1 (Clinic; Study Day -42 to -41):	Table 1: Schedule of Assessments 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).** Table 6: Time Windows for Assessments Visit 1 (Clinic; Study Day **-43 to -42 or** -42 to -41):

Rationale: Collection of blood sample for epilepsy genotype panel is mandatory but not required at screening.

Original Text	**Amendment Text**
Table 1: Schedule of Assessments Epilepsy genotype panel X	Table 1: Schedule of Assessments Epilepsy genotype panel l **l. Mandatory one time collection any time during or after screening.**

Rationale: Added the list of countries in which Diacomit® (stiripentol) is approved.

Original Text	**Amendment Text**
Section 1.1.1, Existing Treatment for Dravet Syndrome To date, only one treatment, Diacomit® (stiripentol) is approved, and only in Europe as adjunctive therapy in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome), and must be co-administered with clobazam and valproate. Stiripentol has not been approved for use in the United States of America, but is available under compassionate use protocols at certain clinical sites.	Section 1.1.1, Existing Treatment for Dravet Syndrome To date, only one treatment, Diacomit® (stiripentol) is approved, and only in Europe, **Canada, Japan, and Australia**, as adjunctive therapy in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome), and must be co-administered with clobazam and valproate. Stiripentol has not been approved for use in the United States of America, but is available under compassionate use protocols at certain clinical sites.

Rationale: Added a supporting reference to an existing citation of data.

Original Text	**Amendment Text**
Section 1.5, Existing Treatment for 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 treatment of DS; the efficacy and safety of this therapeutic approach have been published in a peer reviewed journal and reported to be very favorable. There are no treatments specifically approved for the treatment of DS in the United States of America (USA). Accordingly, there remains an unmet need for an approved treatment for children with DS.	Section 1.1.1, Existing Treatment for 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 treatment of DS; the efficacy and safety of this therapeutic approach have been published in a peer reviewed journal (**Ceulemans 2012; Ceulemans 2016**) and reported to be very favorable. There are no treatments specifically approved for the treatment of DS in the United States of America (USA). Accordingly, there remains an unmet need for an approved treatment for children with DS.

Rationale: Revised the preclinical data section.

Original Text	**Amendment Text**
Section 1.3, Preclinical Data The pharmacokinetics of fenfluramine, norfenfluramine	Section 1.3, Preclinical Data The pharmacokinetics of fenfluramine,

and their respective isomers has been studied in mice, rats, dogs and humans. The pharmacokinetics 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 pharmacokinetics and metabolism of fenfluramine after oral administration. In humans, fenfluramine is metabolized to norfenfluramine. CYP2C19 and CYP2D6 appear to be the predominant CYP enzymes that metabolize fenfluramine to norfenfluramine. CYP1A2, CYP2B6 and CYP3A4/5 also appear to be involved, but to a lesser degree. In vitro inhibition and induction studies show that both fenfluramine and norfenfluramine cause inhibition of CYP2D6, while fenfluramine causes induction of CYP3A4 and CYP2B6. Based on the FDA's mechanistic static model, ZX008 is predicted to potentially cause clinically significant inhibition of CYP2D6 in the range of doses that will be administered (ZX008 IB 2016). ZX008 is also predicted to cause a clinically significant induction of CYP3A4 in most of the doses that will be administered. The major metabolite norfenfluramine, however, is not expected to cause clinically significant inhibition or induction of CYP2B6, 2D6 or 3A4.	norfenfluramine and their respective isomers has been studied in mice, rats, dogs and humans. The pharmacokinetics 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 pharmacokinetics and metabolism of fenfluramine after oral administration. In humans, fenfluramine is metabolized to primarily norfenfluramine. ~~CYP2C19~~ **CYP1A2, CYP2B6 and** CYP2D6 appear to be the predominant CYP enzymes that metabolize fenfluramine to norfenfluramine. ~~CYP1A2, CYP2B6 and CYP3A4/5~~ **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 nordexfenflurmaine (7%-8%) from the body. Because fenfluramine and its active metabolite norfenfluramine have multiple pathways of elimination, interference with a single pathway is unlikely to cause a significant change in fenfluramine's clearance though the probability of an interaction increases if multiple elimination mechanisms are affected simultaneously. ~~In vitro inhibition and induction studies show that both fenfluramine and norfenfluramine cause inhibition of CYP2D6, while fenfluramine causes induction of CYP3A4 and CYP2B6. Based on the FDA's mechanistic static model, ZX008 is predicted to potentially cause clinically significant inhibition of CYP2D6 in the range of doses that will be administered (ZX008 IB 2016). ZX008 is also predicted to cause a clinically significant induction of CYP3A4 in most of the doses that will be administered. The major metabolite norfenfluramine, however, is not expected to cause clinically significant inhibition or induction of CYP2B6, 2D6 or 3A4.~~ **While in vitro studies showed that both fenfluramine and norfenfluramine cause weak inhibition of CYP2D6 and fenfluramine causes weak induction of CYP3A4 and CYP2B6, further analysis based on the FDA's mechanistic static model shows that fenfluramine and its major metabolite norfenfluramine are unlikely to alter the pharmacokinetics of substrates of these CYP450 enzymes in the range of ZX008 doses that will be administered in this study.**
Rationale: Added a supporting reference to an existing citation of data.	
Original Text	**Amendment Text**
Section 1.5, Rationale for Current Study Based on several published reports of fenfluramine's successful treatment of refractory childhood epilepsy in the	Section 1.5, Rationale for Current Study Based on several published reports of fenfluramine's successful treatment of refractory childhood epilepsy

1980s (Aicardi and Gaustaut 1985; Aicardi 1988) and its successful treatment of 11 refractory pediatric epilepsy patients in Belgium (Boel 1996), in 2002 Drs. Ceulemans and Lagae were granted authorization to prescribe fenfluramine to their patients with refractory pediatric epilepsy conditions, including DS, under an approved protocol under a Belgium government program (Royal Decree). To date, these pediatric neurologists have DS patients (infants, children, young adults, and now also adults), being successfully treated with fenfluramine for over 27 years. The efficacy and safety of this therapeutic approach has been reported to be overwhelmingly favorable. In the most recent assessment of efficacy of these patients reported by the investigators in, the average length of treatment was over 12 years, with one patient being successfully treated for 26 years. Of the 15 DS treated patients, 10 (67%) were reported as seizure-free, with the average time of seizure-freedom being 6 years (range 1-19 years). Twelve patients (87%) had a greater than 90% reduction in seizure frequency and 14 patients (93%) with greater than 70% reduction in seizure frequency.	in the 1980s (Aicardi and Gaustaut 1985; Aicardi 1988) and its successful treatment of 11 refractory pediatric epilepsy patients in Belgium (Boel 1996), in 2002 Drs. Ceulemans and Lagae were granted authorization to prescribe fenfluramine to their patients with refractory pediatric epilepsy conditions, including DS, under an approved protocol under a Belgium government program (Royal Decree). To date, these pediatric neurologists have DS patients (infants, children, young adults, and now also adults), being successfully treated with fenfluramine for over 27 years. The efficacy and safety of this therapeutic approach has been reported to be overwhelmingly favorable. In the most recent assessment of efficacy of these patients reported by the investigators in, the average length of treatment was over 12 years, with one patient being successfully treated for 26 years (**Ceulemans 2016**). Of the 15 DS treated patients, 10 (67%) were reported as seizure-free, with the average time of seizure-freedom being 6 years (range 1-19 years). Twelve patients (87%) had a greater than 90% reduction in seizure frequency and 14 patients (93%) with greater than 70% reduction in seizure frequency.
Rationale: Clarified the safety objective.	
Original Text	**Amendment Text**
<u>Synopsis and Section 2.4, Safety Objective</u> To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day to placebo with regard to AEs, laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate [HR], temperature, and respiratory rate), ECGs, ECHOs, and body weight. Cognitive Function will be assessed in subjects 5 years and older using the cognition domain score on the QOLCE. Cognitive function will be assessed using age-appropriate versions of the BRIEF.	<u>Synopsis and Section 2.4, Safety Objective</u> To compare the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day to placebo with regard to AEs, laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate [HR], temperature, and respiratory rate), ECGs, ECHOs, and body weight. **Cognitive Function will be assessed using the cognition domain score on the QOLCE and age-appropriate versions of the BRIEF.** ~~Cognitive Function will be assessed in subjects 5 years and older using the cognition domain score on the QOLCE. Cognitive function will be assessed using age-appropriate versions of the BRIEF.~~
Rationale: Clarify that the number of participating study centers is approximately 30.	
Original Text	**Amendment Text**
<u>Section 3.4, Number of Study Centers</u> The study expects to use up to 30 research centers in Europe, Australia, and South Korea. Additional study centers within or outside of Europe, Australia, and South Korea may be added if enrollment cannot be completed in a timely manner.	<u>Section 3.4, Number of Study Centers</u> The study expects to use up to **approximately** 30 research centers in Europe, Australia, and South Korea. Additional study centers within or outside of Europe, Australia, and South Korea may be added if enrollment cannot be completed in a timely manner.
Rationale: Clarified the duration of use of contraception after the last dose of study drug and added barrier method to the list of acceptable methods of birth control.	
Original Text	**Amendment Text**

Section 4.4 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 effective contraception from the time of informed consent until 90 days after study discharge. 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 30 days following the last follow up visit. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: Progestogen-only hormonal contraception associated with inhibition of ovulation	Section 4.4 Male subjects who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception from the time of informed consent until 90 days **after the last dose of study drug** ~~after study discharge~~. Female subjects who are sexually active and are of childbearing potential must use, with their partner, an approved method of highly effective contraception from the time of informed consent until ~~30 days following the last follow up visit~~ **90 days after the last dose of study drug**. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation **and a barrier method (i.e., condom for male partner)**: Progestogen-only hormonal contraception associated with inhibition of ovulation **and a barrier method (i.e., condom for male partner)**:
Rationale: Removal of social media policy.	
Original Text	**Amendment Text**
Section 4.5 The subject or members of the subject's immediate family (including grandparents) violate the Social Media policy as described in Section 4.9. Section 4.9 Revelations about clinical trial participation and the effect(s) of unapproved study medications can influence the expectations of potential new study subjects and investigators. Throughout their participation in this trial, subjects, their parent/caregivers and immediate family members, including grandparents, can acknowledge participation in the study on social media; however, they will be required not to divulge suspected or actual IMP (ZX008 or placebo), dose, efficacy, or tolerability as it can negatively affect the sponsor's ability to interpret study results and possibly to use the study for registration. Individuals with serious and/or repeated violations of this policy may be required to exit the study at the discretion of the sponsor in consultation with the principal investigator, without the possibility of entering the separate open-label extension study.	Section 4.5 ~~The subject or members of the subject's immediate family (including grandparents) violate the Social Media policy as described in Section 4.9.~~ Section 4.9 ~~Revelations about clinical trial participation and the effect(s) of unapproved study medications can influence the expectations of potential new study subjects and investigators. Throughout their participation in this trial, subjects, their parent/caregivers and immediate family members, including grandparents, can acknowledge participation in the study on social media; however, they will be required not to divulge suspected or actual IMP (ZX008 or placebo), dose, efficacy, or tolerability as it can negatively affect the sponsor's ability to interpret study results and possibly to use the study for registration. Individuals with serious and/or repeated violations of this policy may be required to exit the study at the discretion of the sponsor in consultation with the principal investigator, without the possibility of entering the separate open-label extension study.~~
Rationale: Revised the prohibited concomitant medication and foods list, including Appendix 1.	
Original Text	**Amendment Text**
Section 5.7.4 Drugs/foods that potentially interact with ZX008 via the CYP2D6, CYP3A4, and/or CYP2B6 pathways: A list of medications/foods that are to be avoided as ongoing medications or for chronic use if initiated during the study	Section 5.7.4 ~~Drugs/foods that potentially interact with ZX008 via the CYP2D6, CYP3A4, and/or CYP2B6 pathways:~~ A list of medications/foods that are to be avoided as ongoing medications or for chronic use if initiated

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. Appendix 1: replaced, edits not shown herein.	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. Appendix 1: replaced, edits not shown herein.
Rationale: Clarify the window for assessments (Table 6).	
Original Text	**Amendment Text**
Section 6, Table 6 Visit 3 (Clinic; Study Day ± 4 days[a]	Section 6, Table 6 Visit 3 (Clinic; Study Day ~~-~~ ± ~~+~~ 4 days[a]
Rationale: Clarify the timing of procedures during the baseline period and screening period.	
Original Text	**Amendment Text**
Section 6.1 The Baseline Period of the study encompasses the screening activities that will occur on Study Day -42 and Study Day -41 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. With the exception of the Doppler ECHO, which may be completed any time during the Baseline Period up to Study Day -21, all screening assessments will be completed on Study Day -42 and Study Day -41. The following procedures will be performed during the Screening visit, which will occur between Study Day -42 and Study Day -41 for all subjects before the start of seizure activity observation:	Section 6.1 The Baseline Period of the study encompasses the screening activities that will occur on Study Day -42 ~~and Study Day -41~~ 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. ~~With the exception of the Doppler ECHO, which may be completed any time during the Baseline Period up to Study Day -21, all screening assessments will be completed on Study Day -42 and Study Day -41.~~ ~~The following procedures will be performed during the Screening visit, which will occur between Study Day -42 and Study Day -41 for all subjects before the start of seizure activity observation:~~ **The Screening visit will occur on Study Day -42; however, the procedures may be split over 2 consecutive days (e.g., 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:**
Rationale: Added text clarifying procedures for rescreening.	
Original Text	**Amendment Text**
Section 6.1.1 None.	Section 6.1.1 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 re-screened 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.
Rationale: Clarify timing of dosing on Day -1 and Day 1.	
Original Text	**Amendment Text**
Section 6.1.3 • Dispense study medication Section 6.2.1 Subjects will begin dosing with IMP in the morning of Titration Period Study Day 1.	Section 6.1.3 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.) Section 6.2.1 Subjects will take their first dose of study medication on the morning of Study Day 1. Study Day 1 is considered the first day of dosing, even for those subjects that received an in-clinic dose on Study Day -1. ~~Subjects will begin dosing with IMP in the morning of Titration Period Study Day 1.~~
Rationale: Revised estimated blood volume collection in Table 8 and text describing volumes for collection.	
Original Text	**Amendment Text**
Section 6.5 The original Table 8 was replaced; edits to this table are not shown herein. The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately 108.7 mL, as outlined in Table 8.	Section 6.5 The original Table 8 was replaced; edits not shown herein. A new table, Table 9, showing the priorities for blood collection was added. The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately ~~108.7~~ **99.7** mL, as outlined in Table 8. ***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 43/Visit 8 the pharmacokinetic 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 9:**
Rationale: Clarification of SE as an AE or SAE.	
Original Text	**Amendment Text**
Section 7.1.1 Seizures that evolve into SE will be captured by type and duration (>10 min) as are all seizures. The diagnosis of SE 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. 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.	Section 7.1.1 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 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 (e.g. 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.
Rationale: Clarify SAE reporting.	
Original Text	**Amendment Text**
Section 8.6 For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the AE page of the eCRF. An electronic document containing the AE page and other applicable pages of the eCRF must be sent (via facsimile or email) to the sponsor together with a **Notification of Serious Adverse Event at Investigator Site** cover page, which has been signed and dated by the investigator. If an electronic document is not able to be generated (eg, internet access problem), a handwritten paper SAE report must be completed, which must be signed and dated by the investigator.	Section 8.6 ~~For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the AE page of the eCRF. An electronic document containing the AE page and other applicable pages of the eCRF must be sent (via facsimile or email) to the sponsor together with a **Notification of Serious Adverse Event at Investigator Site** cover page, which has been signed and dated by the investigator. If an electronic document is not able to be generated (eg, internet access problem), a handwritten paper SAE report must be completed, which must be~~

All SAEs that occur during the course of the study, whether or not causally related to IMP must be reported immediately via telephone and either facsimile or email (within 24 hours of the investigator becoming aware of the event) to the sponsor and the Medical Monitor.	~~signed and dated by the investigator.~~ In the event of a 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 iHC 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. Any SAE that occurs 15 days after the last dose of study drug or the last visit, whichever is later that is considered to be causally related to IMP must be reported immediately (i.e., within 24 hours of the investigator becoming aware of the event) to the sponsor and the Medical Monitor.
Rationale: To evaluate a correlation between study drug and SAE.	
Original Text	**Amendment Text**
Section 8.9 None.	Section 8.9 **In the event of a SAE a blood sample for ZX008 and AED PK should be collected as soon as feasible.**