16.1.9 Documentation of Statistical Methods

This section contains:

Statistical Analysis Plan (Studies ZX008-1501 & ZX008-1502) dated 19 September 2017

STATISTICAL ANALYSIS PLAN

Zogenix International Limited
A subsidiary of Zogenix, Inc.
5858 Horton Street, Suite 455
Emeryville, CA 94608 USA

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

A Statistical Analysis Plan Prepared Prospectively to Report Results from Study 1: 120 Subjects Entered into Zogenix Protocols ZX008-1501 and ZX008-1502

Version 2.1 Final
September 19, 2017

Prepared by:

Michael Lock, Ph.D. and Gail Farfel, Ph.D.
Zogenix International, Limited

STATISTICAL ANALYSIS PLAN

SIGNATURE PAGE

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A Statistical Analysis Plan Prepared Prospectively to Report Results from Study 1: 120 Subjects Entered into Zogenix Protocols: ZX008-1501 and ZX008-1502

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19 Sept 2017

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Approval Date

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19 SEP 2017

Michael Lock, PhD
Statistician on Behalf of
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Approval Date

STATISTICAL ANALYSIS PLAN
Zogenix International Limited
ZX008 Study 1

REVISION HISTORY

- Statistical Analysis Plan Study 1 and 2, DRAFT 1.0 13 Sept 2016
- Statistical Analysis Plan Study 1, version 2.0 10 August 2017
- Statistical Analysis Plan Study 1, version 2.1 19 September 2017

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVATION	DEFINITION
AE	Adverse Event
AED	Antiepileptic Drug
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
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
CDISC	Clinical Data Interchange Standards Consortium
CGI	Clinical Global Impression
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-related quality of life
ET	Early Termination
FDA	U.S. Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HR	heart rate
IDSMC	Independent Data Safety Monitoring Committee
IMP	Investigational Medicinal Product
IPCAB	International Pediatric Cardiology Advisory Board
IVR	Interactive Voice Randomization
IWR	Interactive Web Response (System)
kg	kilogram
kg/ m^2	kilogram per meter square
MCSF	mean convulsive seizure frequency
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg/day	milligram per kilogram per day
min	minute(s)
mITT	modified Intent-to-Treat
mL	milliliter
MMRM	Mixed Effects Model for Repeated Measures

ABBREVATION	DEFINITION
msec	millisecond
PedsQL	Pediatric Quality of Life Inventory
PD	pharmacodynamic
PDCO	Pediatric Committee of the European Medicines Agency
PK	pharmacokinetic
PP	Per Protocol
QoL	Quality of Life
QOLCE	Quality of Life in Childhood EpilepsyQuality of Life
QTcF	corrected QT interval using Fredericia method
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SMEI	Severe Myoclonic Epilepsy Of Infancy
SOC	System Organ Class
T+M	Titration plus Maintenance Periods (14 wks, randomized treatment period)
TEAE	Treatment Emergent Adverse Event
THC	Tetrahydrocannabinol
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization Drug Dictionary
ZX008	Proprietary name for Fenfluramine Hydrochloride

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SCOPE

Zogenix is conducting two identical Phase 3 studies of ZX008, Study ZX008-1501 (Study 1501) and Study ZX008-1502 (Study 1502). Study 1501 is being conducted in the United States and Canada; Study 1502 is being conducted in Europe and Australia. Approximately 120 subjects with Dravet syndrome, a rare form of pediatric epilepsy, are planned for randomization into each study in three treatment groups: 0.2 mg/kg/day ZX008, 0.8 mg/kg/day ZX008 and placebo (n=40/group). Due to slow enrollment into both trials, the databases for the two trials will be combined and the first 120 subjects to be randomized will be analyzed and reported as Study 1, covered by this Statistical Analysis Plan (SAP). Additional randomized subjects (over N=120) are intended to be reported as Study 2, and a separate SAP will cover those analyses. Primary and key secondary analyses in the Study 1 SAP remain as stated in the protocols and as described in the Study 1 draft SAP with some changes delineated in this SAP based on FDA feedback.

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1. INTRODUCTION

ZX008 (low dose 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). DS is a highly treatment-resistant and refractory epilepsy 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.

Zogenix is developing a new formulation of fenfluramine hydrochloride, ZX008, for the adjunctive treatment of DS. The clinical development plan includes two identical Phase 3 studies for ZX008, Study 1501 and Study 1502. Study 1501 is being conducted in the US and Canada and Study 1502 is being conducted in Europe and Australia. Both studies are multicenter, double-blind, parallel-group, and placebo-controlled, designed to assess the efficacy, safety, and pharmacokinetics (PK) of ZX008 when used as adjunctive therapy in pediatric and young adult subjects with DS. Within each study subjects who qualify for entry will be randomized (1:1:1) in a double-blind manner to receive either a low dose of ZX008 (0.2 mg/kg/day), a high dose of ZX008 (0.8 mg/kg/day), or placebo. The pre-specified efficacy, safety, and PK objectives and endpoints for both studies are identical.

This Statistical Analysis Plan (SAP) is based on the protocols for Study ZX008-1501 version 3.0 dated Oct 31, 2016, and Study ZX008-1502 version 2.0 dated Oct 31, 2016, which are identical in design, conduct, and randomization scheme. Due to slow enrollment into both trials, the databases for the two trials will be combined and the first 119 subjects to be randomized will be analyzed and reported as Study 1, covered by this Statistical Analysis Plan (SAP). Additional randomized subjects (over N=120) are intended to be reported as Study 2, and a separate SAP will cover those analyses. Primary and key secondary analyses in the Study 1 SAP remain as stated in the two protocols and as described in the draft Study 1 SAP with some changes based on FDA feedback.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of Study 1 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 Study 1 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 ≥50% reduction from baseline in convulsive seizure frequency.
    - The longest convulsive seizure-free interval.

2.3 ADDITIONAL SECONDARY OBJECTIVES

- 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 ≥25%, or ≥75% reductions from baseline in convulsive seizure frequency.
    - The change from baseline in non-convulsive seizure frequency.
    - The change from baseline in convulsive + non-convulsive seizure frequency
    - The incidence of rescue medication usage
    - The incidence of hospitalization to treat seizures
    - The incidence of status epilepticus.

- 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.
    - The change from baseline in the Pediatric Quality of Life Inventory™ (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 Hospital Anxiety and Depression Scale (HADS).

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2.4 SAFETY OBJECTIVE

The safety objective of the Study 1 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 bodyweight. Cognitive function will be assessed using age-appropriate versions of the Brief Rating Inventory of Executive Function (BRIEF).

2.5 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objective of Study 1 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 1 is:

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

3. STUDY DESIGN

3.1 OVERALL STUDY DESIGN AND PLAN

Both Study 1501 and Study 1502 are multicenter, double-blind, parallel-group, placebo-controlled studies designed to assess the efficacy, safety, and PK of ZX008 when used as adjunctive therapy in pediatric and young adult subjects with Dravet syndrome. Study 1501 will be conducted at approximately 30 study sites in North America; Study1502 will be conducted at approximately 30 study sites in Europe and Australia. Study 1501 and Study 1502 are being conducted in parallel; thus, combining subjects from the two identically designed studies enables an earlier evaluation of the safety and efficacy of ZX008 than analysis at the time of full enrollment of each study independently. This earlier analysis enables an earlier determination of the benefit-risk profile of ZX008, to minimize the total subject exposures should the risk-benefit profile not be positive.

The expected study period of 22 weeks comprises a Baseline period (6weeks), a Treatment period (14weeks) (2 weeks titration + 12 weeks maintenance), and a Post Dosing visit 2 weeks after study completion or early termination.

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. There will be cardiac safety follow-up of 3 to 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. Subjects from France, Germany and the Netherlands will have a CV follow-up visit approximately 24 months after the last dose of active study medication. Follow safety visit results will be reported separately.

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, with the target of 25% of subjects 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. The randomization scheme and block size for Studies 1501 and 1502 are the same, so combination of the data from the two studies will not skew the intended randomization into the three treatment groups.

Study 1 will include the first 120 randomized subjects from Study 1501 and Study 1502. Once enrollment in Study 1 is complete (i.e., when subjects 1 to 120 are randomized), the subjects will be treated and followed through their last study visit. After the last of the subjects in Study 1 has either discontinued or completed treatment, the database will be locked for those subjects and Study 1 be reported as per this SAP.

3.2 TREATMENT ARMS

Treatment ARM A: ZX008 0.2 mg/kg/day

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.

ZX008 0.2 mg/kg/day will be divided into two daily doses up to a maximum of 30 mg/day.

Treatment ARM B: ZX008 0.8 mg/kg/day

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.

ZX008 0.8 mg/kg/day will be divided into two daily doses up to a maximum of 30 mg/day.

Treatment ARM C: Placebo

Placebo 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

Placebo will be given twice daily.

3.3 TREATMENT PERIODS

Titration Period:

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 Investigational Medicinal Product (IMP) will be based on the randomized dose and subject's weight at Visit 3 (Day -1). At Visit 8 (Day 43), if the subject's weight has changed ±25% of the weight at Day-1, the IMP dose will be recalculated. Subjects will be dosed using the oral dosing syringe provided.

In order to maintain the blind across all dose groups 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 (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 Day 9, the dose for the 0.8 mg/kg/day group will increase to the target dose. The titration is expected to take a total of 14 days (Table 2). A new bottle of IMP will be started by the subject at each level of the titration step.

Table 2: 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.			

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.

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 from 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 will 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 30mg/day). After 4 days at this dose level (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 Day 9, all subjects will stop taking study medication. The taper is expected to take a total of 8 days (Table 3). A new bottle of IMP will be started by the subject at each level of the taper step.

Table 3. 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.		

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 4). 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.

Table 4. 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.

Data from the Taper or Transition period will not be included towards the planned efficacy endpoints except where specified, but will be included in the safety analyses.

3.4 RANDOMIZATION

Treatment assignments are assigned independently within Study 1501 and Study 1502. Specifically, each trial assigns treatments using randomized permuted blocks; i.e., treatments are assigned in blocks to ensure exact balance among treatments within each block. The blocking is applied across the entire trial such that newly enrolled subjects are randomized to the next available treatment regardless of the site or country where they enroll. This approach assures balance among treatment groups within each trial at any point during enrollment. Combining data from two trials means that two sets of randomized blocks will be used, which would have approximately the same effect as doubling the block size in a single trial. Increasing the block size is expected to have little impact on a trial of 120 subjects. Moreover, combining the first 120 randomized subjects from Study 1501 and Study 1502 to create Study 1 preserves balance among the three treatment groups in each of Study 1 and Study 2, yielding approximately 40 subjects per arm, the number required to maintain full statistical power.

4. SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Post-Dosing	Cardiac Follow-up
Study Assessments	**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 to -41**	**-21**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**3-24 mo post dose**
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													
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		

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Table 1: Schedule of Assessment (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	**-42 to -41**	**-21**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**3-24 mo post dose**
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.
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 if warranted 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
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.

5. ANALYSIS POPULATIONS

5.1 ENROLLED POPULATION

The Enrolled Set includes all subjects who signed the informed consent form. This population will be used to present overall study disposition data and the number of subjects in each study population.

5.2 RANDOMIZED POPULATION

The Randomized Set includes all subjects randomized to receive study treatment. This is the Intention-to-treat (ITT) population.

5.3 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 group to which they were randomized.

5.4 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.

5.5 PER PROTOCOL (PP) POPULATION

The PP Population includes all randomized subjects who receive at least one dose of ZX008 or placebo, complete at least 4 weeks of the Maintenance Period, and have no important protocol deviations that would have a significant impact on clinical outcome. Subjects will be analyzed according to the treatment group to which they were randomized. Protocol deviations will be reviewed and the list of deviations warranting exclusion from the PP Population will be finalized prior to study unblinding.

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.

6. STATISTICAL METHODOLOGY

6.1 STATISTICAL AND ANALYTICAL ISSUES

6.1.1 Statistical Methods

Tabulations for Study 1 will be produced for appropriate demographic, baseline, efficacy and safety parameters. Continuous data will be summarized using descriptive statistics including the number of observations, 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 described in the sections below.

All efficacy parameters will be summarized by descriptive statistics. Two-sided statistical significance testing (alpha level = 0.05) comparing each active treatment to placebo will be performed for the primary and secondary endpoints as described below, unless otherwise noted.

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.3, unless otherwise noted). Adverse events will be coded using the most recent MedDRA version available at the time of analysis. Concomitant medications will be coded using the most recent version of World Health Organization (WHO) Drug.

6.1.2 Multiplicity Strategy and Testing Hierarchy

Multiplicity issues in the statistical inference in this study arise from two sources: (a) multiple treatment comparisons, and (b) multiple endpoints.

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.

All statistical analyses will be performed and results tabulated with test statistics, p-values, and/or 95% confidence intervals.

Formal statistical testing will be performed for 1 primary endpoint and 2 secondary endpoints, for the comparison of ZX008 0.8 mg/kg with Placebo, and between ZX008 0.2 mg/kg with Placebo. Hence there are 6 formal hypothesis tests: 1 primary hypothesis test and 5 secondary hypothesis tests. To preserve the overall Type 1 error rate at α=0.05, these tests will proceed as follows:

Step 1: The primary efficacy endpoint (mean convulsive seizure frequency per 28 days) will be formally tested first between the 0.8 mg/kg and Placebo group. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 2. Otherwise formal testing of the other hypotheses stops.

Step 2: The secondary efficacy endpoint, the proportion of subjects who achieve a ≥50% reduction from baseline in convulsive seizure frequency, will be compared between the 0.8 mg/kg and Placebo group. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 3. Otherwise formal testing of the other hypotheses stops.

Step 3: The endpoint, the longest convulsive seizure-free interval will be compared between 0.8 mg/kg and Placebo. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 4. Otherwise formal testing stops.

Step 4: The mean convulsive seizure frequency per 28 days will be formally tested first between the 0.2 mg/kg and Placebo group. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 5. Otherwise formal testing of the other hypotheses stops.

Step 5: The secondary efficacy endpoint, the proportion of subjects who achieve a ≥50% reduction from baseline in convulsive seizure frequency, will be compared between the 0.2 mg/kg and Placebo group. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 6. Otherwise formal testing of the other hypotheses stops.

Step 6: The endpoint, the longest convulsive seizure-free interval will be compared between 0.2 mg/kg and Placebo using a significance level of α=0.05 (2-sided).

6.1.3 Subgroups

Select efficacy and safety outputs may be further broken down by the following subgroups:

- Age strata: <6 years, ≥6 years.

6.1.4 Baseline Definition

Baseline	Baseline period consists of 42 days immediately preceding first administration of study treatment. Any assessment performed during these 42 days before first administration of study treatment will be considered for baseline assessment. Study day 1 will be the first day of study drug administration, which is either the date of randomization, or the day after the randomization date. For the change in the frequency of convulsive seizures endpoint, baseline will include all data from the baseline period of 42 days immediately preceding Day 1(Visit 3). For all other endpoints, baseline is the last non-missing result from the Baseline period prior to receipt of the first administration of study treatment.

6.1.5 Other Definitions

Treatment completers are those subjects that are compliant with IMP at least 85% of dosing days and fulfill at least one of the following criteria:

- Subjects that did not discontinue from the trial prior to end of study visit at Day 99 ± 4 days (Visit 12).
- Subjects that complete the Treatment Period T+M starting from study Day 1 (Visit 3) through the protocol defined end of study visit at Day 99 ± 4 days (Visit 12).
- Subjects that enroll in the open label extension study.

6.1.6 Visit Windows and Period Start/Stop Dates

The following rules will be used to window data into treatment periods for by treatment period tabulations. For all by-visit tabulations, the nominal visit as recorded on the CRF will be used.

Double Blind Treatment Period	The Double-Blind Treatment Period start date is the date of first dose. The Double-Blind Treatment Period end date is the last date the patient was on study treatment. The Double-Blind Treatment Period consists of 16 weeks from first treatment start date, which includes 2 weeks of Titration period, 12 weeks of Maintenance period and 2 weeks of Taper/Transition period, therefore the end date would be considered the date at Visit 13.

	For subjects who discontinue early from the study, the double-blind treatment period end date will be the date at the early termination visit (Visit 12).
Titration Period	The Titration Period covers the first 14 ± 4 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 Visit 6 (when the patient has reached their randomization dose). The Titration Period applies to all subjects including placebo recipients. If a subject withdraws from the study prior to treatment in the maintenance period, all safety assessments and events up to and including the date of study withdrawal will be tabulated in the titration period.
Maintenance Period	The Maintenance Period covers the 12 weeks following the end of the titration period. It begins on the date of Visit 6 + 1 day and extends through the end of study/early termination visit (Visit 12).
Titration + Maintenance Period (T+M)	The T+M period combines the Titration and Maintenance periods, beginning on the date of first treatment (Study Day 1) and extending the end of study/end of treatment visit. The T+M period is considered the treatment period.
Taper/Transition Period	The Taper/Transition period consists of 2 weeks starting from end of study/early termination visit (Visit 12) + 1 day. For patients who are not entering into the open-label extension study, patients will gradually be tapered off of study medication. For patients who are entering the open-label extension study, patients will enter the transition phase where all patients will be on a dose of 0.2mg/kg/day at the end of this phase. The end date of this period is considered to be the date recorded at Visit 13.

6.1.7 Handling of Dropouts and Missing Data

There will be no imputation of missing data for efficacy endpoints.

Seizure Diaries:

Seizures are recorded in the Daily Seizure Diary (DSD), while the End of Day Diary (EDD) provides Yes/No confirmation that that seizures were experienced for a specific date, or that the date was seizure free.

- If no seizures are entered in the DSD and the EDD confirms seizure freedom, the number of seizures for that date is zero.
- If seizures are entered in the DSD and the EDD states seizure freedom, the seizures recorded for that date supersede the EDD stating seizure freedom.
- If no seizures are entered in the DSD and there is no response in the EDD, that day will be considered to have missing diary data.
- If no seizures are entered in the DSD and there is a Yes response in the EDD, that day will be considered to have missing diary data.

Handling of missing date information for AEs:

- The term *missing date* refers to a completely missing date or to an incomplete date/partial date where parts are not available, e.g. missing month/day/year.
- Missing start and end date will be imputed conservatively, i.e. missing values will be imputed in such a way that the duration of the AE is considered with the longest possible duration and such that, whenever the AE may potentially start after first IMP, the AE will be handled as a TEAE.
- The missing start date and End date of AE will be imputed for the purpose of calculating treatment emergent status and assigning events to treatment periods using definitions given in the following table.

	Adverse event
Partial /Missing Start date	Missing day – If Adverse event day is missing but month and year is present then Impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date. Missing day and month – If adverse event day and month both missing but year is present then impute 1st January unless year is the same as first dose date then impute first dose date. Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date. When imputing a start date, ensure that the new imputed date is sensible i.e. is prior to the end date of the AE.

	Adverse event
Partial /Missing End date	Missing day – If AE end day is missing but month and year are present then Impute the last day of the month unless month is same as month of last dose of study drug then impute last dose date. Missing day and month – If AE has missing day and month but year is present then impute 31st December unless year is the same as first dose date then impute last dose date. Completely Missing – need to look at whether the AE is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present (i.e. do not impute a date). If the AE has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is after the last dose date.

6.1.8 Conversion of time interval

In case a time interval was calculated in days and needs to be converted into weeks, months or years the following conversion factors need to be used:

1 week = 7 days

1 month = 30.4 days

1 year = 365.25 days

6.1.9 Pooling of Investigative Sites

There are approximately 60 sites participating in Studies 1501 and 1502 from US, Canada, Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden, United Kingdom and Australia. Approximately 35 sites will contribute randomized subjects to Study 1. It is likely that the number of patients recruited by some sites will be small. The primary analysis will use data pooled across sites. Differences among regions may be explored if warranted.

6.1.10 Determination of Sample Size

The sample sizes for Zogenix Studies 1501 and 1502 were calculated based on the results of two trials with stiripentol reported in the European Public Assessment Report (EPAR) for stiripentol (EMA, 2007). The stiripentol 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 Protocols 1501 and 1502 that compares 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 yielded a requirement for an additional 35 subjects in the 0.2 mg/kg/day ZX008 group. The total sample size for each study was therefore set at 105 subjects.

In December 2016 results from a double-blind, placebo-controlled Phase 3 study with Epidiolex to treat seizures in Dravet syndrome were presented at the American Epilepsy Society Meeting (http://ir.gwpharm.com/events.cfm). In the Epidiolex study, active drug reduced seizures by 39% compared to a reduction of 13% in the placebo. Review of the data suggested that the standard deviation was relatively large, likely above 50% in both treatment groups. In consideration of this new data, the sample size was re-estimated for the ZX008 studies to assume a SD of 55%, higher than the previous estimate of 50%. Other assumptions in the sample size calculation remained unchanged. A sample size of approximately 120 subjects (40 per arm) affords 90% power to detect a difference in mean change from baseline of 40 percentage points with 55% SD. Considering the variability seen in the STILCO and Epidiolex trials, the sample size for Study 1 and Study 2 is set at 120 subjects, 40 per treatment arm. Note that the change in assumed SD was based entirely on data from external trials. Efficacy data from both Study 1501 and 1502 are still blinded and were not used in re-estimating the required sample size.

The enrollment for Study 1 will consist of the first 120 subjects to be randomized into either Study 1501 or Study 1502. Study 1 will be analyzed per this prospectively prepared Statistical Analysis Plan for Study 1; Version 2.0. Subjects who withdraw early will not be replaced. Subjects who are randomized into Study 1501 or Study 1502 after the first 120 randomized subjects will be analyzed in Study 2, per a separate statistical analysis plan.

6.2 SUBJECT CHARACTERISTICS

6.2.1 Subject Disposition

Subject disposition will be presented per treatment group and overall.

For describing the subject disposition, the following will be summarized by number and percentage:

- Subjects enrolled (only overall)
- Subjects enrolled but not randomized and reason for not-randomized (only overall)
- Subjects randomized
- SAF
- mITT
- PP
- Subjects assigned to SAF, mITT, PP and discontinued the study and reason.
- Number of subjects in the trial per trial period/phase (Titration Phase, Maintenance Phase, Follow-up Period) will be presented for SAF and mITT sets.
- Trial completers.
    - Trial completers continuing in the open-label extension study
    - Trial completers not continuing in the open-label extension study

For subjects enrolled but not randomized to treatment and for the reasons for not being randomized the denominator used to calculate the percentage will be the number of enrolled subjects. For all other calculations the denominator will be the number of subjects randomized.

All subject data will be listed using the enrolled population and sorted by treatment and site.

6.2.2 Protocol Deviations

Major protocol deviations will be summarized overall and by site based on the SAF. Major protocol deviations are those that have the potential to impact patient safety or affect data integrity. Major protocol deviations will be grouped into categories and may include categories such as

- Violation of inclusion/exclusion criteria
- Violation of randomization inclusion criteria
- Time schedule deviations of IMP
- Non-compliance regarding intake of IMP
- Inappropriate intake of concomitant medication
- Missing essential data
- Subject not discontinued as per protocol
- Other non-compliance

Multiple deviations can occur in the same subject and thus a subject can be counted in more than 1 deviation category.

Major and minor protocol deviations will be presented in a subject data listing for the all enrolled population, sorted by treatment and site.

6.2.3 Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized descriptively per treatment group and overall, for the SAF and mITT populations.

6.2.3.1 Subject Demographics

The following demographic characteristics will be summarized:

- Age[Years]
- Categorical age as <6 years and ≥6 years.
- Sex
- Race
- Ethnicity
- Height [m]
- Weight [kg]
- BMI [kg/m^2]

All subject demographics data will be listed for the enrolled population.

6.2.3.2 Other Baseline Characteristics

Epilepsy/seizure history and epilepsy genotype panel data will be descriptively summarized as per data type (categorical). Genetic data will be summarized as the proportion who have or do not have mutations of the SCN1A gene. Additional analyses of genetic data will be prepared in a separate report.

All subject baseline characteristics will be listed for the enrolled population.

6.2.4 Treatment Exposure and Compliance

6.2.4.1 Treatment Exposure

Treatment exposure data will be summarized and analyzed for the SAF population.

Duration of total exposure to fenfluramine hydrochloride (i.e., time on treatment (in days)) will be calculated per subject as the number of days with IMP intake during the trial, and will be summarized using n, mean, standard error, median, minimum, Q_1, Q_3 and maximum.

This will be calculated as:

Date of last IMP intake – Date of first IMP intake + 1

Time on treatment will be summarized by treatment group.

6.2.4.2 Compliance

Study medication is to be administered twice daily, and compliance is recorded in the eDiary as full (both doses), partial (less than full daily dose) or missed (both doses) each day. From this,

compliance will be calculated by assuming that a missed dose=0% of dose consumed, partial=50% of dose consumed, and full=100% of dose consumed. For each subject, a daily compliance score will be thus obtained.

Compliance will be summarized for the SAF and mITT populations over the course of T+M and Maintenance only, reported by treatment group.

6.2.5 Prior and Concomitant Medications and Therapies

Medication (collected on the prior/concomitant medication eCRF page) will be coded using the World Health Organization Drug Dictionary (WHO-DD).

The following algorithm will be used to define prior and concomitant:

Concomitant medications will be defined as those medications that were initiated after study drug administration or those that were ongoing at the time of study drug administration.

The medication will be assumed to be prior medication if it cannot be definitively shown that the medication did not start or continue during the treatment period.

If the start date or stop date of a medication is partially missing, the date will be compared as far as possible with the date of the start of administration of study drug. The following approach will be taken:

- If the start date of medication is complete and occurs on or after the day of the first dose, the medication will be assumed concomitant. If the start date occurs prior to the first dose date but the end date is on or after the first dose date or the medication is recorded as ongoing, the medication will be considered concomitant.
- If the start day is missing but the start month and year are complete, a medication will only be excluded as being concomitant if the start month/year is before the month/year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration.
- If the start day and month are missing but the start year is complete, a medication will only be excluded as concomitant if the start year is before the year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration.
- If the start date is completely missing and the stop date is prior to first dose or completely missing, the medication will be assumed to be a prior medication.

Medication will be summarized and sorted alphabetically separately for prior and concomitant medication by Anatomical Therapeutic Chemical (ATC) categories (Level 2: pharmacological or therapeutic subgroup and Level 3: chemical or therapeutic or pharmacological subgroup) and WHO-DD drug code. For each medication the number and percentage of subjects will be displayed.

Summary tables will be presented on SAF population.

All prior and concomitant medications/treatments will be listed for the enrolled population.

6.2.6 Prior and Concomitant Antiepileptic Treatment

Treatments (collected on the prior/concomitant antiepileptic treatment eCRF page) will be coded using the World Health Organization Drug Dictionary (WHO-DD).

Prior and concomitant antiepileptic will be defined and analyzed for the SAF similar to concomitant medications as described in section 6.2.5.

All prior and concomitant antiepileptic treatments will be listed for the enrolled population.

6.2.7 Medical History

Medical history will be summarized and sorted alphabetically, by primary System Organ Class and Preferred Term coded via the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects will be displayed for each System Organ Class and Preferred Term within treatment group.

Medical history will be presented for the SAF population.

All prior and concomitant medical history data of subjects will be listed for the enrolled population.

6.3 EFFICACY ANALYSIS

The analysis of the primary and secondary efficacy parameters will be performed on the mITT population, except where noted.

The primary and key secondary efficacy analyses will be repeated on the PP Population if there are substantial differences between the makeup of the mITT and PP population, in order to assess the impact of major protocol deviations on the key inference.

All primary and key secondary variables will be analyzed for data obtained for the T+M period, and will be repeated for data obtained during the M period only.

6.3.1 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. For each subject, the CSF will be calculated from all available data collected during the Baseline and T+M Periods, and the treatment group mean convulsive seizure frequency per 28 days (MCSF) will be calculated for the baseline and T+M period.

The baseline period is the 42 days immediately preceding the Randomization visit and the T+M period is planned for 14 weeks. However, actual durations will be computed for each subject based on the individual subject's start and stop dates for each period, except that if the baseline period is longer than 42 days, the average for the baseline period will be taken over the 42 days immediately preceding the Randomization visit.

The convulsive seizure frequency will be counted from the daily diary records provided by the Subject or Parent/Caregiver.

For any individual subject, the convulsive seizure frequency per 28 days during the baseline period (CSF_B) will be derived as follows:

$$CSF_B = \frac{28 \times \text{Total number of convulsive seizures during the Baseline Period}}{\text{Total number of days in the Baseline Period with nonmissing diary data}}$$

For each treatment group, the mean is obtained by averaging over the subjects in the treatment group.

Similarly, for each subject, the convulsive seizure frequency per 28 days for the T+M period ($MCSF_{T+M}$) is derived as below:

$$CSF_{T+M} = \frac{28 \times \text{Total number of convulsive seizures in the T + M period}}{\text{Total number of days in the T + M period with nonmissing diary data}}$$

The percentage change from baseline for any individual subject will be estimated by

$(CSF_{T+M} - CSF_B)*100/CSF_B$

The difference from baseline will be estimated by $CSF_{T+M} - CSF_B$.

Corresponding treatment group means are designated with "M" preceding the quantity. For each treatment group, descriptive statistics for MCSF during baseline, T+M and M only, as well as the differences and % changes from baseline, will include the number of observations, mean, standard deviation, median, minimum and maximum, overall and by age group (<6 years, ≥6 years).

6.3.1.1 Primary Analysis

T+M Period:

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.

The primary endpoint (CSF_{T+M}) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group (three levels) and age group (< 6 years, ≥6 years) as factors, log baseline CSF_B as a covariate and log CSF_{T+M} as response. Treatment group mean differences from placebo will be estimated via least squares means from the analysis model along with 95% confidence intervals and associated 2-sided p-values. Estimated treatment differences and CI endpoints will be exponentiated for presentation.

The nullhypothesis

$$H_0: \mu_{Z0.8} - \mu_P = 0,$$

will be tested against the alternative

$$H_A: \mu_{Z0.8} - \mu_P \neq 0,$$

where $\mu_{Z0.8}$ and μ_P represent the ZX008 0.8 mg/kg and Placebo group means (on the log scale), respectively.

Rejection of the null hypothesis in favor of the alternative, in the presence of a statistically significantly smaller mean convulsive seizure frequency for the treatment group compared to the placebo group, (two-sided p-value < 0.05) will be regarded as evidence of a treatment benefit in favor of the 0.8 mg/kg group.

Sample SAS code for the ANCOVA described above is as follows:

```
proc glm data=temp;
        class agegrp trtp;
```

```
model csftm = bcsf agegrp trtp  / SS3;
lsmeans  trtp / pdiff stderr;
```

where trtp = randomized treatment group (with codes 1, 2, 3 indicating placebo, 0.2 mg, and 0.8 mg groups).

bcsf = log(CSF_B),
csftm = log(CSF_{T+M} + 1)
agegrp = age group.

Additional statements may be used to obtain estimates and associated 95% confidence intervals. Endpoints of the CIs may be exponentiated to obtain CI on the original scale. Fitted values and residuals may be plotted to check model assumptions.

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 ANCOVA will be used to analyze the data, with ranks of the baseline CSF_B as a covariate and ranks of CSF_{T+M} as response, and the results will be used to assess the primary objective. If normality assumptions are not met, the results of the nonparametric test will be used to assess the primary objective.

M Period only:

The primary analysis described above will be repeated using data from the Maintenance period only as response. For subjects who did not reach the Maintenance period, their Transition period data will be used to represent their M period data.

A similar ANCOVA model will be used, and if distributional assumptions are not met, a nonparametric analysis will be performed.

Treatment by baseline seizure category interaction: The primary analysis described above will be repeated with baseline seizure frequency as a categorical variable, rather than a covariate. Baseline seizure frequency per 28 days will be categorized as either < 10; 10-50; or >50.

6.3.1.2 Supplementary and Sensitivity Analyses

Impact of AED Medications

Subjects in the study are required to be on stable background therapy. An additional analysis will be performed to assess the impact on the primary analysis of changes in dose or type of concomitant AED medications, which are protocol violations, that may occur during the course of the study. Specifically, the percentage of subjects who had a change in dose or type of concomitant AED medication will be compared between treatments. For this analysis, each subject will be classified according to whether the subject had a change in the prescribed dose or type of concomitant AED medication during the T+M period. Fisher's exact tests will be used to compare the active dose group with the placebo group.

Per protocol Analysis

Additionally, the primary efficacy analysis will be repeated on the per protocol population (which excludes subjects with important protocol deviations that may affect the inference on efficacy such as a change in dose or type of concomitant AED medication).

Percentage Reduction from Baseline

The ANCOVA employed in the primary analysis uses log CSF_{T+M} as the response adjusts for baseline seizure frequency by incorporating CSF_B as a factor in the model. The alternative approach described here calculates the percentage change in CSF from baseline directly and uses that quantity as the response variable in an ANCOVA model. Specifically, the ANCOVA will use the percentage change from the T+M period to baseline as the response variable, baseline CSF as a covariate, and treatment and age stratum as classification factors. The analyses will be repeated for the M period only using the baseline as covariate.

If the distributional assumptions for the parametric analysis are not met, a nonparametric ANCOVA will be used for the ranks of the dependent variable as response, using the ranks of the baseline as covariate.

Criteria for Establishing Efficacy

While several supportive and/or supplementary analyses are specified above, the main criterion for demonstrating efficacy will be the primary analysis using the log transform for the mITT population. It is conceivable that some or all of these supplemental analyses may not reach statistical significance. However, it is expected that the direction of effect will be in favor of the test treatment. As an example, a statistically significantly smaller least squares adjusted MCSF for the treatment group compared to placebo, in the presence of a smaller proportion of subjects on 0.8 mg/kg than Placebo subjects increasing their dose of concomitant AEDs will be strong evidence for efficacy of the experimental treatment.

6.3.2 Key Secondary Analysis

6.3.2.1 MCSF for ZX008 0.2 mg/kg/day versus Placebo

The MCSF during the T+M period will be analyzed and compared between the ZX008 0.2 mg/kg/day group and the placebo group using the same methods employed for the primary analysis. Following the same strategy as the ZX008 0.8 mg/kg/day comparison, a nonparametric analysis using ranks will be used for the ZX008 0.2 mg/kg/day comparison if the assumptions of the parametric ANCOVA model are not met.

The analysis will be repeated for the M period.

Similar supplementary analyses will be performed as for the comparison of the 0.8 mg/kg group with placebo.

6.3.2.2 Proportion with ≥50% Reduction from Baseline in Convulsive Seizure Frequency

Subjects with a percent reduction in convulsive seizures of at least 50 percentage points from baseline will be identified and the overall proportion within each treatment tabulated. That is, the proportion of subjects in the ZX008 0.8 mg/kg/day group who have a decrease in convulsive frequency of at least -50 percentage points will be compared to the analogous proportion in the placebo group.

Similarly, the proportion of subjects in the ZX008 0.2 mg/kg/day group who have a change in convulsive frequency of at least -50 percentage points will be compared to the analogous proportion in the placebo group.

The comparison between treatment groups will be made using a logistic regression model that incorporates the same factors as the ANCOVA used in the primary analysis. This will model a categorical response variable (achieved 50 percentage point reduction, yes or no) as a function of treatment group (ZX008 and placebo) and age group (< 6 years, ≥6 years).

Raw descriptive statistics will be presented by treatment group, and will include the number and proportion of subjects < 6 years, ≥6 years, and overall achieving the reduction along with the model estimated odds ratio (including a 95% confidence interval) and p-value for comparison of ZX008 0.8mg/kg/day to placebo and ZX008 0.2mg/kg/day to placebo separately.

6.3.2.3 Longest Interval between Convulsive Seizures

The longest interval between convulsive seizures will be analyzed.

For each subject, the longest interval between convulsive seizures will be calculated over the entire T+M period. This will be derived as the maximum of the number of days between consecutive convulsive seizures. The intervals between consecutive convulsive seizures will be calculated as below, after which the longest interval between convulsive seizures will be derived.

If a subject has two consecutive days of missing diary data, the current seizure-free interval will be ended on the first date of missing diary data, and a new one begun on the next date that diary data are available and no seizure occurs. [In that case, for purpose of calculation of this variable, all intervening days, after the 2nd day, with missing diary data, will be assumed to have a convulsive seizure occurrence, until the first available date with non missing diary data.]

Let Date0 (=Day1) be the first day of treatment. If convulsive seizure occurs on five days having dates as Date1, Date2, Date3, Date4 and Date5, where Date5>Date4>Date3>Date2>Date1≥Date0, and let LDT = Last date of treatment in the maintenance period, where LDT ≥ Date5, then the time interval between convulsive seizures will be calculated as follows:

I1=Date2 - Date1

I2=Date3 - Date2

I3=Date4 – Date3,

I4=Date5 – Date4.

For completeness, we calculate the time to the first seizure as

I0=Date1 – Date0,

and the time from the last seizure to end of treatment as

I5 = LDT – Date5.

Here the duration of the longest interval =Maximum (I0, I1, I2, I3, I4, I5).

If the subject does not experience a seizure during treatment, then the last available diary date will be used to compute the duration of the longest interval as follows:

The longest interval=last available diary date – Date0

The median time of the longest convulsive seizure-free interval will be presented. Additional summary statistics will be presented, including mean, minimum, maximum, the 25th and 75th percentiles, 95% confidence intervals on the difference in medians between groups (Hodges-Lehman estimator).

The Wilcoxon rank sum test will be used to test for differences between each treatment arm and placebo, and the p-value from this test will be presented. A histogram presenting the percentage of subjects whose longest seizure free interval is <10, 11-20, 21-40, 41-60, 61-84, and ≥84 days will accompany all descriptive statistics and all data will be provided in a data listing.

6.3.3 Additional Secondary Endpoint Analysis

6.3.3.1 Number of Convulsive Seizure Free Days

Convulsive seizure free days will be taken from the parent/caregiver diary data.

A convulsive seizure free day will be defined as a day for which diary data are available and no convulsive seizures have been reported. The total number of convulsive seizure free days will be summed for the entire T+M period and similarly for the baseline period.

Seizure free days per 28 days at baseline = (number of seizure free days during baseline)*28/(number of days during baseline with non-missing diary data)

Seizure free days per 28 days during T+M Period = (number of seizure free days during T+M Period)*28/(number of days during T+M Period with non-missing diary data)

Statistical comparison of treatment groups and placebo on the number of seizure free days per 28 days during T + M using the baseline as covariate will be done with a similar approach as the primary analysis.

6.3.3.2 Responder Analyses: Proportion with ≥25, or 75% Reduction from Baseline in Convulsive Seizure Frequency

A response curve will be generated for the mITT population. This graph will plot the % of subjects (y-axis) against percentage reduction in seizure frequency per 28 days in the T+M period (x-axis). The horizontal axis will be the % reduction, and the vertical axis will be the % of subjects achieving ≥ that % reduction. In the graph, subjects experiencing an increase or no decrease in seizure frequency (i.e., ≤0 % reduction) will be regarded as having a 0% reduction in seizure frequency. Hence the ordinate for the 0 time point may not necessarily be at 100%. For example, if 15% of subjects have no reduction in seizure frequency during T+M period compared to the baseline period, the graph will start on the y-axis at 85%. The graph will be generated for all subjects, by treatment group.

- The proportion achieving a ≥25% reduction from baseline in convulsive seizures will be analyzed for both treatment groups (ZX008 0.2 mg/kg/day and ZX008 0.8 mg/kg/day)

comparing independently with placebo, using the same method employed for the ≥50% reduction from baseline endpoint.

- The proportion achieving a ≥75% reduction from baseline in convulsive seizures will be analyzed for both treatment groups (ZX008 0.2 mg/kg/day and ZX008 0.8 mg/kg/day) comparing independently with placebo, using the same method employed for the ≥50% reduction from baseline endpoint.

A second response curve will be generated in which subjects who experience an increase in seizure frequency will be represented on the curve at horizontal axis at the position representing their increase in seizure frequency. Increases in seizure frequency will be represented to the left of the vertical axis on the figure.

6.3.3.3 Change from Baseline in Non-Convulsive Seizure Frequency

Algorithms for calculating mean non-convulsive seizure frequency and percent change from baseline will follow the methods as described for the primary endpoint using a nonparametric ANCOVA to analyze the data, with ranks of the baseline non-CSF_B as a covariate and ranks of non-CSF_{T+M} as response,.

Change from baseline in non-convulsive seizures will be presented by seizure types (e.g., focal, generalized).

6.3.3.4 Change from Baseline in Convulsive + Non-Convulsive Seizure Frequency

The change from baseline in convulsive + non-convulsive seizure frequency will be calculated as described for the primary endpoint, but considering both convulsive and non-convulsive seizures.

Algorithms for calculating mean convulsive and non-convulsive seizure frequency and percent change from baseline will follow the methods as described for the primary endpoint using a nonparametric ANCOVA to analyze the data, with ranks of the baseline convulsive + non-CSF_B as a covariate and ranks of convulsive + non-CSF_{T+M} as response,

6.3.3.5 Incidence of Rescue Medication Usage

Use of rescue medication is recorded on the daily diary. In the event of prolonged seizures or status epilepticus, rescue medication is administered according to each subject's personalized regimen consisting of one or more medications. If the first rescue administration does not control the seizures, a second or even third round might be administered. They second and third round might use different medications or different doses than the first round of rescue meds.

Rescue medication will be summarized by treatment group and by active treatment vs. Placebo for the following:

- The number of days rescue medication was taken (normalized to 28 days) will be summarized separately for the Baseline and T+M periods by the mean (SD) as well as the median and range. Multiple medications taken on the same day will be counted once for that day. The ZX008 group will be compared to the placebo group using a rank ANCOVA analogous to that described in Section 6.3.1.1. Specifically, the rank ANCOVA will use the ranks of rescue medication frequency during T+M as the response, and will incorporate treatment group as a factor and the ranks of rescue medication frequency during Baseline as a covariate.

- The number of medications used per episode will be summarized using similar descriptive statistics as above. Rescue medications related to an episode of SE are considered to be all rescue administered on the day of the SE (or seizure lasting >10 min). If more than one episode of SE or a seizure lasting >10 min occurred in a single day, the rescue medication for that episode is all rescue administered after the seizure until the start time of the next prolonged seizure.

6.3.3.6 Incidence of Hospitalization to Treat Seizures

Hospitalization data will be captured in the CRF and will be used to calculate incidence.

The number and percentage of subjects who utilized medical center care to treat a seizure will be presented by treatment group for the T+M period. Statistical comparisons of the differences between treatment and placebo groups will be based on Cochran-Mantel-Haenszel test stratified by age group.

6.3.3.7 Incidence of Status Epilepticus

The incidence of status epilepticus will be evaluated based on cases captured as such with treatment at hospitals or other treatment centers, those entered as adverse events (including SAEs) into the safety database, and also as convulsive seizures lasting longer than 10 min from the seizure diary. A single seizure meeting more than one of these criteria will be counted once. According to the ILAE, seizures of this duration are to be considered SE.
The number and percentage of subjects with status epilepticus recorded as an AE will be presented by treatment group for the baseline and the T+M period per 28 days. Statistical comparisons of the differences between treatment and placebo groups will be based on Fisher's exact test.

In addition, from the diary data, change from baseline in the number and percentage of convulsive seizures with duration >10 min for the baseline and T+M period will be reported. The number and percentage of subjects will be presented by treatment group for the baseline and the T+M period per 28 days. Statistical comparisons of the differences between treatment and placebo groups will be based on Fisher's exact test.

All seizures recorded in the AE database as status epilepticus should also be included in the seizure diary. An edit check will be performed to identify the overlap between seizures identified as AE of SE and seizures entered into the diary as seizures > 10 min. The "calculated" number and percentage of subjects experiencing SE will be presented by treatment group, defined as individuals who experience either an AE of SE, medical treatment for SE, or a seizure lasting longer than 10 min. Each subject will be represented once regardless of incidence. Statistical comparisons of the differences between treatment and placebo groups will be based on Fisher's exact test.

A second calculation will present the number of incidences of SE, according to the above definition, by treatment group normalized to per 28 days. In this analysis, a single subject may have more than one episode of SE, but an episode of SE recorded as both an AE and as a seizure longer than 10 min will be counted as a single episode. Statistical comparisons of the differences between treatment and placebo groups will be based on Fisher's exact test.

6.3.3.8 Duration of Prolonged Seizures

Duration of convulsive seizures at baseline and on treatment will be presented by treatment group using categories as <2 min, 2-10 min and >10 min.

To obtain a baseline probability distribution for the 3 categories, we will proceed as follows: For each subject, we will calculate the percentage of their total number of baseline seizures that is in each category. (For example, if the subject had 5 seizures, with 2 in the first category and 3 in the last category, their percentage distribution would be 40%, 0%, and 60% in the <2, 2-10, and >10 categories. We can calculate similar numbers for the next subject, and so on.) We will then average these over all subjects to obtain the % of subjects' seizures that were <2 min in duration, the % between 2-10 min in duration, and the % >10 min in duration. These 3 percentages should total 100%. Thus we will obtain a distribution of seizure duration for baseline.

Using the seizure duration data obtained for the T+M period, we will proceed similarly, to obtain a distribution for the T+M period.

It is expected that treatment with ZX008 will result in shorter duration of seizures (as well as fewer seizures) during T+M compared to placebo, i.e., the probability of longer seizures (>10 min) will be higher for the placebo group than for the ZX008 arms. This may be assessed by comparing the probability of a >10 min seizure during T+M to the same during baseline, for a treatment group, to the same for the Placebo group. It is expected that the ZX008 group will have greater odds of a reduction in proportion of seizures >10 min than the Placebo group. However, treatment with ZX008 may result in fewer seizures overall yet the duration of residual seizures may not be shorter. Should the primary or key secondary endpoints be positive for a given dose(s), but the duration of seizures not be shortened per above, exploratory evaluations may be undertaken to better understand the effect.

6.3.3.9 Clinical Global Impression – Improvement Rating, as assessed by the Parent/Caregiver

The parent/caregiver and the investigator will rate their global impression of the subject's condition at each clinic visit after randomization: end of Titration period (Visit 6), Maintenance period (Visit 8 and 10), and at End of study (Visit 12).

The CGI-I scale measures the change in the subject's clinical status from a specific point in time, i.e., the Baseline Period. The CGI-I 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 mean (SD) CGI-I score, and the number and percentage of subjects who showed improvement (i.e., had a score of 3 or lower), and the number and percentage who did not improve (i.e., had a score of 4 or higher) will be presented for each for each treatment group at

each assessment timepoint. Each assessment time point will also include a comparison between each active treatment and the placebo group using the Cochran-Mantel-Haenszel test stratified by age group, and a frequency distribution of the number and percentage of subjects in each category in the scale. A histogram of the frequency distribution will be presented.

The number and percentage of subjects who showed good or very good improvement (i.e., had a score of 2 or lower), and the number and percentage who did not improve (i.e., had a score of 3 or higher) will also be presented for each for each treatment group at each assessment timepoint as an exploratory analysis.

Individual subject CGI data will be listed.

6.3.3.10 Clinical Global Impression – Improvement Rating, as assessed by the Principal Investigator

CGI-I score data assessed by the principal investigator will be summarized and analyzed using the same methods used for CGI-I score data recorded by parent/caregiver as above.

6.3.3.11 Quality of Life in Childhood Epilepsy (QOLCE) Scale

The parent/caregiver will complete this questionnaire for the QOLCE. This assessment 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, at baseline period (Visit 3), at Maintenance period (Visit 8) and at End of study/ET (Visit 12). There is also one question on overall quality of life, administered as part of the QOLCE.

The QOLCE scores items with a possible 5 point response. To calculate subscale scores, the 5 point item scores will first be reverse coded as necessary so that scores of 5 represent the best possible response and 1 represents the worst possible response. Item scores will then be transformed to a 0-100 scale as follows: 1-0, 2-25, 3-50, 4-75, 5-100. After transformation, the subscales are computed by averaging across subscale items. Subscale scores are then averaged to obtain an overall quality of life score. The higher the subscale and overall quality of life scores, the better the response.

Table 2: Subscale of QOLCE:

Domain	Subscale	Item
Section 3: Physical	Physical Restrictions	3.1 a-j
Section 3: Physical	Energy/Fatigue	3.2 a,b
Section 4: Well-being	Depression	4.1 a,d,e,l
Section 4: Well-being	Anxiety	4.1 b,g,j,n,o,p
Section 4: Well-being	Control/helplessness	4.1 c,f,h,i
Section 4: Well-being	Self-esteem	4.1 k,m,q,r,s
Section 5: Cognition	Attention/Concentration	5.1 a,d,e,f,g
Section 5: Cognition	Memory	5.1 j,k,l,m,n,o
Section 5: Cognition	Language	5.1 p,q,r,s,t,u,v,w
Section 5: Cognition	Other Cognitive	5.1 b,c,h
Section 6: Social Activities	Social Interactions	6.1 c,f,h
Section 6: Social Activities	Social Activities	6.2, 6.3, 6.4

Section 6: Social Activities	Stigma Item	6.1 i
Section 7: Behavior	Behavior	7.1 c,f,g,h,i,j,k,l,m,o,q,r,s,t
Section 8: General Health	General Health	8.1
Section 2 (USA Version) or Section 9 (Australia Version)	Overall quality of life	2.1 or 9.1

For each treatment group at Baseline and End of Study/ET, the mean (SD) score will be presented for each QOLCE subscale and for the overall quality of life score.

In addition, the change from baseline in the overall QOLCE will be calculated for each subject by subtracting the baseline overall score from the overall score measured at End of Study/ET. The change from baseline for each treatment group will be summarized by the mean (SD) and treatment groups will be compared using pairwise Wilcoxon tests.

Individual subject data for the domains will be listed.

6.3.3.12 Quality of Life of the Parent/Caregiver using EQ-5D-5L Scale

The impact on the quality of life of the parent/caregiver responsible for a patient with DS will be assessed at Baseline (Visit 3) and at End of study (Visit 12) using the EQ-5D-5L. The responsible parent/caregiver was permitted to opt out of completing the EQ-5D-5L.

The EQ-5D-5L health questionnaire is a health-related quality of life instrument with 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 possible levels: no problems, slight problems, moderate problems, severe problems and extreme problems.

The summary of results will follow the EQ-5D-5L guideline results presentation. For the “Health Profiles” descriptive system summary results will show the number, and proportion (%) of subjects in each Item score (No Problems, Slight Problems, Moderate Problem, Severe Problem, Extreme Problems) by treatment at baseline and at the end of study. In addition, the item scores will be classified into two categories as “No Problems” and “Problems,” the latter comprised of slight, moderate, severe and extreme problems. Summary results will show number of patients and proportion (%) with “No Problems” and with “Problems” by treatment at baseline and at end of study.

For the VAS measure of overall self-rated health status, descriptive statistics summary results will be presented for the VAS score showing number of subjects, mean, standard deviation, median, and range by each treatment at baseline and end of study time points.

The change from baseline in VAS will be calculated by subtracting the VAS score at baseline from the VAS score obtained at End of Study/ET. The change in VAS will be summarized using descriptive statistics, and treatment groups will be compared using pairwise Wilcoxon tests.

The quality of life of parent/caregiver individual data will be listed using EQ-5D-5L scale.

6.3.3.13 Parent/Caregiver Assessment using HADS Scale

The HADS is a tool commonly used to determine the levels of anxiety and depression that a person is experiencing and is administered to the primary parent/caregiver to assess these

symptoms longitudinally during the study. The responsible parent/caregiver was permitted to opt out of the HADS. The HADS is a 14-item scale that generates ordinal data for two dimensions: 1) Anxiety and 2) Depression. Seven of the items relate to anxiety and 7 relate to depression. Each item has 4 possible answers rated 0-3. All answers to the items for a dimension with their respective rating are added resulting in a range for each dimension from 0-21. Scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress.

Summary descriptive statistics including the mean and SD will be generated separately for the Anxiety and Depression dimensions at both Baseline and at End or Study/ET. In addition, each subject will be categorized at each time point based on the score cut-offs below which were validated on adult patients in a treatment setting.

Score	Category
0-7	Normal
8-10	Borderline abnormal
11-21	Abnormal

Summary statistics will include number and proportion (%) of subjects in each of the categories above at each study visit.

In additional, the total score for Anxiety and Depression will be generated. Descriptive statistics summaries including mean, median, standard deviation, median and range will be summarized for each treatment at Baseline and End of Study/ET.

The change from baseline for each subject will be calculated by subtracting the total Anxiety and Depression score measured at Baseline from the analogous score measured at End of Study/ET. The change from baseline will be summarized by descriptive statistics and the difference between treatment groups will be assessed using pairwise Wilcoxon tests.

The individual item outcomes will be presented in the subject data listing.

6.3.3.14 Pediatric Quality of Life Inventory (PedsQL 4.0 Generic Core) Scale

The PedsQL 4.0 is a quality of life scale that measures four functional areas (physical, emotional, social, and school functioning). The scale is available in age-appropriate instruments with child self-report and parent proxy-report formats. In this study, the age appropriate categories for the administration of the instrument were ages 2-4, 5-7, 8-12 and 13-18 years, and the Parent Reports were used.

There are 8 items for Physical Functioning, and 5 questions each for Emotional, Social, and School Functioning. Each of the responses to the 23 items is initially scored on a 5 point Likert scale from 0 (Never) to 4 (Almost always). Scores will be linearly transformed to a scale of 0 to 100, where 0=100, 1=75, 2=50, 3=25 and 4=0, and higher scores mean better health related quality of life. If more than 50% of the items in the scale are missing, the scale scores should not be computed. A mean score is calculated as the sum of the items over the number of items answered. If some of the answers on a scale are missing but 50% or more of the items in the scale are completed, then impute the mean of the completed items in a scale. The scaled results will be combined across age categories to produce a single score for each functional area.

A Psychosocial Health Summary score is computed as the sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales.

A Physical Health Summary score is made up of the Physical Functioning Scale Score.

The Total Score is computed as the sum of all the items over the number of items answered on all the Scales.

Descriptive statistics at both Baseline and EOS/ET will be provided for the Psychosocial Health Summary score, the Physical Health Summary score and Total Score.

The change from baseline for the Total Score will be calculated for each subject by subtracting the Total Score measured at Baseline from the Total Score measured at End of Study/ET. The change from baseline will be summarized with descriptive statistics and treatment groups will be compared on the Total Score using pairwise Wilcoxon tests.

6.3.3.15 Pediatric Quality of Life Inventory (PedsQL 2.0 Family Impact Module) Scale

The PedsQL™ Family Impact Module was designed to measure the impact of pediatric chronic health conditions on parents and the family. The PedsQL™ Family Impact Module measures parent self-reported physical, emotional, social, and cognitive functioning, communication, and worry. The Module also measures parent-reported family daily activities and family relationships.

There are 6 items for Physical Functioning, 5 items each for Emotional Functioning, Cognitive Functioning and Worry, 4 for Social Functioning, and 3 for Communication. There are additionally 3 questions for Daily Activities and 5 for Family Relationships.

Each of the responses to the 36 items is initially scored on a 5 point Likert scale from 0 (Never) to 4 (Almost always). Scores will be linearly transformed to a scale of 0 to 100, where 0=100, 1=75, 2=50, 3=25 and 4=0, and higher scores mean better health related quality of life. If more than 50% of the items in the scale are missing, the scale scores should not be computed. A mean score is calculated as the sum of the items over the number of items answered. If some of the answers on a scale are missing but 50% or more of the items in the scale are completed, then impute the mean of the completed items in a scale.

The Parent HRQL Summary Score (20 items) is computed as the sum of the items divided by the number of items answered in the Physical, Emotional, Social, and Cognitive Functioning scales.

The Family Functioning Summary Score (8 items) is computed as the sum of the items divided by the number of items answered in the Daily Activities and Family Relationships scales.

The Total Score is the sum of all 36 items divided by the number of items answered.

Descriptive statistics for baseline and EOS/ET will be provided for the summary scores.

6.3.4 Exploratory Analyses

Exploratory analysis may be performed by comparing of ZX008 0.2 and 0.8 mg/kg/day doses on primary, secondary, safety and PK endpoints.

Thus, all comparisons planned for ZX008 to placebo may be repeated to compare the ZX008 0.2 and 0.8 mg/kg/day doses.

Additional exploratory analyses may include descriptive summaries of the primary endpoint by:

- genetic mutation data
- seizure type
- baseline seizure frequency
- Age (greater than or equal to 13 years at baseline)

6.4 SAFETY ANALYSIS

All safety analyses will be performed for the Safety population as defined in Section 5.3 (SAF) and will be reported by treatment group as well as ZX008 combined for the 16-week treatment period unless noted otherwise.

6.4.1 Adverse Events

An AE is defined as 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 the titration/transition period (Visit 13). For patients who continue into the open-label extension study, AEs of special interest will continue to be monitored for up to 6 months after the last dose of study medication.

A TEAE is defined as any AE that based on start date information occurs after the first intake of study treatment. Safety tables will present TEAE data by assigned treatment group through Visit 13. All other AEs occurring after enrollment and prior to the first administration of study treatment are defined as non-treatment emergent AEs (non-TEAEs).

AEs are categorized as related or unrelated. If the AE is thought to be definitely, probably or possibly related to study drug then it is to be categorized as related. Possibly or definitely unrelated is categorized as unrelated. Any missing relationship will be considered as "related."

The severity of AEs (whether nonserious or serious AEs) will be assessed by the investigator as follows:

Severity Definition of Adverse Events:

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

Any missing severity will be imputed as "severe."

The original terms used by the investigators in the eCRFs to identify AEs will be coded using the most recent version of the MedDRA implemented by the sponsor at the end of the study.

6.4.1.1 Overview of Adverse Events:

The number and percent of patients with at least one of the following events will be summarized in an overall summary table:

- TEAE.
- Serious TEAE
- Related TEAE
- Related serious TEAE.
- Severe TEAEs
- Adverse events of special interest
- Death

The percentage denominator for the calculation of percentage will be the number of subjects in the SAF.

6.4.1.2 Treatment Emergent Adverse Events

The following summaries will display the number and percentage of subjects with an adverse event as well as the corresponding number of events by system organ class (SOC) and preferred term (sorted alphabetically):

- All TEAEs
- Serious TEAEs
- TEAEs by Maximum Severity
- Study Drug Related TEAEs
- All AEs that lead to premature discontinuation from the study

One additional summary table will tally the number and percent of subjects in each treatment group who experience an AE that occurs in at least 5% of subjects. The summary will be presented by preferred term in decreasing order of incidence.

No inferential statistical methods (i.e., methods that yield p-values) will be used to compare treatment groups on the frequency or severity of AEs.

These summaries will be provided for the T+M period

Additionally, the following listings will be produced for all enrolled subjects:

- All AEs, events considered to be TEAE will be identified in the listing
- Serious AEs
- AEs that lead to premature discontinuation from the study
- Deaths

6.4.2 Adverse Events of Special Interest (AESI)

As per ICH guidance (E2F Development Safety Update Report [2011]), the sponsor has identified the following AESIs for the ZX008 in below table-

Table 5 – 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) • ≥ mild valve regurgitation (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
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

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 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

MedDRA SMQs will be employed as applicable to identify each AESI category or manually assigned through review. This will be completed and documented prior to study unblinding.

Adverse events of special interests will be summarized by treatment group and by system organ class and preferred term for the T+M Period.

All adverse events of special interest will listed separately.

6.4.3 Physical Examination

A complete physical examination will be performed at Screening Visit (Visit 1), day of randomization (visit 3) prior to first dose of study medication, and at the EOS visit. An abbreviated physical exam is performed at Day 15 (Visit 6), 43 (Visit 8), and 71 (Visit 10). A complete or abbreviated physical exam may be performed at the Cardiac follow-up visit for patients who do not enter the open-label extension study if clinically warranted.

All physical examination results will be presented in a subject data listing, including the description of abnormalities. New, clinically meaningful abnormalities will be reported as adverse events.

6.4.4 Neurological Examination

A complete neurological examination will be performed at Screening Visit (Visit 1) and EOS (Visit 13). An abbreviated neurological examination will be performed at randomization (visit 3) and at Visit 6.

Shift tables representing neurological exam results from randomization to EOS will be presented by body system.

All neurological examination results will be presented in a subject data listing, including the description of abnormalities.

6.4.5 Vital Signs, Weight, and BMI

Vital signs data including blood pressure, heart rate, temperature, respiratory rate, weight, and BMI will be documented for subjects during study at screening visit (visit 1), randomization (visit 3) prior to first dose of study medication, titration period (visit 6), and maintenance period (visit 8 and visit 10) and at EOS visit (visit 12).

The mean value and change from baseline to each on-study evaluation will be summarized for vital signs and weight by treatment group. Vital signs, Weight and BMI data will be presented for each patient in a data listing.

For each subject with a clinically meaningful abnormality in vital signs, weight, or BMI (to be supplied by Sponsor), a table will be produced organized by parameter that lists each subject, age, sex, day of most abnormal value, the most abnormal value, and the reference range.

A listing of each subject's values will be created.

6.4.6 Electrocardiogram

12-Lead ECGs data (PR, QRS, QT, QTcF, and HR) will be documented for subjects during study at baseline (Visit 1 and Visit 3), Day 43 (Visit 8), at End of Study (Visit 12) and at Cardiac Follow-up (Visit 14).

Analysis of Echocardiograms will be included in a separate report from Biomedical Systems.

All ECG values will be presented in the subject data listing. In addition to the subject data listing with all ECG values, a listing of all abnormal, clinically relevant findings will be presented organized by subject, by parameter, then by visit.

6.4.7 Doppler Echocardiography

Color Doppler echocardiography (ECHO) will be conducted at a facility with experience for the subject's age at Screening, Maintenance period (Visit 8), End of study (Visit 12), and Cardiac Follow-up (Visit 14). ECHO 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 the below table:

Signs on ECHO indicative of potential Valvulopathy	Normal Values for Children 2-18 years
• valve regurgitation (aortic or mitral) • ≥ mild valve regurgitation (tricuspid, or pulmonary) • Mean Mitral valve gradient ≥ 4 mmHg • Mean Aortic valve gradient ≥ 15 mmHg • Mean Tricuspid valve gradient ≥ 4mmHg • Peak Pulmonary valve gradient ≥ 21mmHg	• No regurgitation • Mean Mitral valve gradient < 4 mmHg • Mean Aortic valve gradient < 15 mmHg • Mean Tricuspid valve gradient < 4mmHg • Peak Pulmonary valve gradient < 21mmHg

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

Results of ECHOs will be presented in a separate report from Biomedical Systems.

6.4.8 Tanner Staging

Tanner Staging will be assessed for subjects >7 years old during the study at baseline period (Visit 3) and End of study (Visit 12). 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 onset and progress of pubertal changes will be recorded on a 5 point scale for boys and girls separately. Boys are rated for genital development and pubic hair growth through stage I to stage V. Girls are rated for breast development and pubic hair growth through stage I to stage V.

The number and percentage of subjects in each Tanner Stage will be presented for all visits by treatment group separately for boys and girls overall and also broken out for the following age groups:
>7years to <=11,
>11years to <=15,
>15years to <=18.

All Tanner staging data will be presented in the subject data listing.

6.4.9 Laboratory Parameters

Laboratory safety parameters will be analyzed by a central laboratory using standard validated methods.

All laboratory safety data will be collected as per the schedule of assessments given in Table 1.

The following continuous laboratory parameters will be analyzed:

- Hematology: hemoglobin, hematocrit, erythrocytes, erythrocyte mean corpuscular volume, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets
- Blood Biochemistry: albumin (ALB), alkaline phosphatase (AP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2), chloride (Cl), creatinine, creatine

kinase, gamma-glutamyl transferase (GGT), globulin, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), thyroid function, 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
- 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

Observed continuous laboratory data will be descriptively summarized by type of laboratory test/parameter by treatment group. Changes from baseline will also be presented for all continuous laboratory parameters by treatment group over time.

Categorical laboratory parameters will be summarized by presenting the number and % of subjects by visit and by treatment arm.

All laboratory values (including invalid values, reference ranges, and possible flags (low, high,)) will be presented in the subject data listings.

A listing of subjects with Potentially Clinically Significant (Extreme) laboratory results will be provided.

6.4.10 Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale data will be collected as per at screening visit (Visit 1), at randomization (visit 3), Titration period (at visit 6), maintenance period (at Visit 8 and 10) and at End of study visit (Visit 12).

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.

All individual subject C-SSRS data will be listed.

Suicidal Ideation:

The following outcomes are C-SSRS categories for suicidal ideation and have binary responses (yes/no):

Category	Outcome Description
1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act
4	Active suicidal ideation with some intent to act, without specific plan
5	Active suicidal ideation with specific plan and intent

Suicidal ideation is assessed as a "yes" answer at any time during the T + M period to any one of the five questions (1-5) above. The number and percentage of subjects with suicidal ideation will be presented, as well as the number and percentage having a "yes" response to each category (1-5) at least once during the T + M period. The denominator will be the number of subjects completing the C-SSRS at least once during the T + M Treatment period.

Suicidal Behavior:

The following outcomes are C-SSRS categories for suicidal behavior and have binary responses (yes/no):

Category	Outcome Description
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt
9	Actual attempt (non-fatal)
10	Completed suicide

Suicidal behavior is assessed as a "yes" answer at any time during the T + M period to any one of the five questions (6-10) above. The number and percentage of subjects who had suicidal behavior, as well as the number and percentage having a "yes" response to each category (6-10) at least once during the T + M period. The denominator will be the number of subjects completing the C-SSRS at least once during the T + M period.

Suicidal Ideation or Behavior:

An overall composite will be provided similar to the suicidal ideation and behavior endpoints, but will instead count a subject if any of the C-SSRS questions 1 through 10 are marked as 'yes' anything during the T+M period.

Self-injurious behavior without suicidal intent:

The number and percentage of subjects having reported anytime during the T+M period experiencing a 'Self-injurious behavior without suicidal intent' event (Question 11) will be provided.

6.4.11 Brief Rating Inventory of Executive Function (BRIEF and BRIEF-P)

The Behavior Rating Inventory of Executive Function (BRIEF™) and its preschool version, BRIEF-P, are standardized, validated rating scales to measure executive function in children within the home and school environments that will be assessed by the parent according to the schedule in Table 1 (i.e. at Randomization (Visit 3), at Maintenance period (Visit 8) and at End of study visit (Visit 12)).

The BRIEF measures multiple aspects of executive functioning; scales include Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor.

The original BRIEF was the basis for the development of the BRIEF-P. The BRIEF-P Rating Form consists of 63 items that measure various aspects of executive functioning: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize.

For the BRIEF and the BRIEF-P, mean scores at Baseline, End of Study/ET and mean change from baseline to End of Study/ET, and descriptive statistics will be presented by treatment group for the Safety population (SAF).

6.5 PK/PD ANALYSIS

The bioanalytical methods for the determination of individual plasma concentrations of fenfluramine and its metabolite (norfenfluramine) will be reported together with the plasma concentration results in separate bioanalytical reports. These bioanalytical reports will be issued as a separate report.

6.6 ANALYSIS OF OTHER ASSESSMENTS

Not applicable

6.7 INTERIM ANALYSIS

No formal interim analysis is planned for Study 1 However, the cohort of subjects that comprise Study 1 are subsets of subjects from Study 1501 and Study 1502.

Unblinding for Study 1 will not occur until data cleaning is completed and all decisions regarding protocol deviations warranting exclusion from the per protocol population have been made. Personnel from the sponsor or any designee who become unblinded for the purposes of data cleaning and database lock for Study 1 will not participate in decision-making regarding subjects' data for Study 2 (the remainder of subjects entering Study 1501 or Study 1502) to avoid any real or apparent bias in such decisions.

6.8 INDEPENDENT DATA SAFETY MONITORING COMMITTEE

The IDSMC is an independent advisory body that monitors participant safety, data quality and progress of all clinical trials. 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 IDSMC will:

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

The list of tables, listings, and figures will be provided to the IDSMC as per IDSMC charter.

6.9 CHANGES TO METHODS PLANNED IN THE PROTOCOL

- The 1501 and 1502 protocols set a target that 40% of enrolled subjects to be less than 6 years old, but candidate subjects have been older than expected. Consequently, the enrollment target has been revised to ensure that at least 25% of subjects are less than 6 years old.
- Protocols 1501 and 1502 state that efficacy and safety endpoints will be repeated separately for the titration and maintenance periods, however this is not planned to be conducted –Data from the T+M Period will be summarized and analyzed for all endpoints, and separate analyses of titration or maintenance periods will be generated only for selected endpoints.
- Protocols 1501 and 1502 state that analyses of safety data will be presented by treatment actually received. However, safety data will be presented by randomized treatment group except where noted otherwise.
- Protocols 1501 and 1502 provide sample size calculations to support a total study sample of 105 subjects, 35 per treatment group. A revised sample size calculation has increased the sample size to 40 subjects per treatment group, for a total of approximately120 subjects.
- Protocols 1501 and 1502 state that a sensitivity analysis for the primary efficacy endpoint will be conducted by adding a factor indicating whether a subject had a change in prescribed dose or type of concomitant AED medication during the T+M Period, however this is not planned to be conducted. Instead it is planned to compare the treatment groups with respect to the proportion of subjects who changed dose and/or type of AED concomitant medication during the T+M Period.
- Protocols 1501 and 1502 state that the longest interval between convulsive seizures will be analyzed using a log-rank test. However, further considerations of this endpoint suggest that while the first seizure-free interval may be subject to independent censoring, the second and later seizure-free intervals are subject to dependent censoring. Moreover, the last seizure-free interval is subject to intercept sampling, hence a longer seizure-free interval is more likely to be censored. Finally, the number of seizures or seizure-free

intervals is informative about the underlying distribution, as subjects at a higher risk of experiencing recurrent events are likely to have shorter and hence more seizure-free intervals during the 84 day treatment period. Thus, a simple analysis comparing medians of the largest seizure free intervals was proposed.

- Responder analyses – Protocols 1501 and 1502 include a ≥40% response analysis as one of the key secondary endpoints. It was decided to not include this endpoint.
- An analysis of the percentage of subjects who achieve a 25% reduction in seizures was added. The number of subjects whose seizures worsen during the study will be included, along with the percentage of worsening.
- The Protocol states that the BRIEF rating scale will be used to evaluate cognition in children aged 2-18. The BRIEF-P will be used for children aged 2-4, and the BRIEF will evaluate children aged 5-18.
- Interim analysis – Protocols 1501 and 1502 do not delineate an interim analysis. However, this Study 1 Analysis Plan is a pooled analysis of data from the first 120 subjects to be randomized into studies 1501 and 1502, in order to assess the benefit and risk at an earlier timepoint than fully recruiting each trial independently. Both studies will continue to enroll, and the remaining approximately 120 subjects will be analyzed as Study 2, under a separate analysis plan.

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8. APPENDICES

APPENDIX 1: LIST OF PLANNED TABLES, FIGURES AND LISTINGS

Table/ Figure/ Listing	Number	Table Header
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Statistical Analysis Plan for Cardiovascular Endpoints

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
Investigational Product:	ZX008
Sponsor Study No.:	ZX008-1501 and ZX008-1502; "Study 1"
SAP Status:	V1.0
Date of SAP:	15 September 2017
SAP Prepared by:	Biomedical Systems
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Abbreviations and Definitions of Terms

ΔΔQTcF	Change from baseline and placebo (Double-Delta) in QTcF
ACI	Abnormal Clinically Insignificant
ANOVA	Analysis of Variance
APCS	Abnormal Potentially Clinically Significant
bpm	Beats per minute
C_{max}	Maximum Plasma Concentration
CI	Confidence Interval
CL/F	Oral dose apparent clearance
DS	Dravet's Syndrome
ECG	Electrocardiogram
E_{max}	Maximum Effect
GSMB	Global Superimposed Median Beat
kg	Kilogram
h, hr	Hour
HR	Heart Rate
ITT	Intention to Treat
m	Minutes
mg	Milligram
mL	Milliliter
mm	Millimeter(s)
mmHg	Millimeters of Mercury
ms	Millisecond(s)
N	Sample Size
ng	Nanogram
PAH	Pulmonary Arterial Hypertension
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PR	Interval between the start of the P wave and start of the Q wave
QRS	QRS waves complex on the electrocardiogram tracing
QT	Interval between the start of the Q wave and the end of the T wave

QTc	Corrected QT duration
QTcF	QT interval corrected using Fridericia's formula
RR	The time interval between consecutive heart beats.
SAP	Statistical Analysis Plan
SD	Standard Deviation
s	Second(s)
SMEI	Severe Monoclonal Epilepsy of Infancy
SUPED	Sudden Infant Death in Epilepsy
t_{max}	Time to maximum concentration (C_{max})
$t_{1/2}$	Half-life associated with terminal phase of the concentration-time profile
TdP	Torsade de Pointes
ZX008	Fenfluramine Hydrochloride

1 Introduction

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 usually live in institutional care homes.

The primary known pharmacologic action of fenfluramine is serotonin release in the CNS (Baumann, 2014); preliminary evidence suggests a role for other mechanisms of action as well. Fenfluramine is readily absorbed after oral administration with an oral bioavailability of 60-70% (Bever and Perry, 1997) and a Tmax of 4 hours (Beckett & Brookes, 1967). Terminal half-life (t1/2) is approximately 20 hours for the parent and 30 hours for the active metabolite, norfenfluramine. Metabolism occurs primarily by Cytochrome P450 (CYP)1A2, CYP2B6 and CYP2D6. CYP2C9, CYP2C19 and CYP3A4 also appear to be involved, but to a lesser degree. Elimination of the drug and its metabolites is largely renal. The drug readily crosses the blood brain barrier and is widely distributed in all tissues.

When fenfluramine was marketed for treatment of obesity at doses of 60-120 mg/day, reports of cardiac valvular disease emerged (Connolly, 1997). The FDA issued an advisory request for information from similar cases and eventually requested voluntary withdrawal of fenfluramine and dexfenfluramine from the market in 1997.

There were 144 individuals reported to have valvulopathy involving fenfluramine or dexfenfluramine in the initial 1997 communication (CDC, 1997). Of 113 confirmed cases, 111 occurred among women; the median age was 44 years (range: 22-68 years). Of these 113 cases, 2 (2%) used fenfluramine alone; 16 (14%) dexfenfluramine alone; 89 (79%) a combination of fenfluramine and phentermine; and 6 (5%) a combination of all 3 drugs. The median duration of drug use was 9 months (range: 1-39 months). Overall, 87 (77%) of the 113 cases were

symptomatic and 24 (27%) required valve replacements.

The prevalence of valve lesions was assessed for patients who were exposed to these drugs but who had no obvious history of cardiac disease or cardiac symptoms in 5 independent unpublished echocardiographic surveys submitted to FDA in 1997. These surveys demonstrated a prevalence of valvular disease meeting the case definition ranging from 30.0% to 38.3% (overall: 32.8%; 95% confidence interval=27.7%-38.9%). However, subsequent studies sought to estimate the risk of valvulopathy in fenfluramine-treated adult obese patients and found fenfluramine-associated valvular disease was less common than the original observational reports suggested, approximately 9.6% for aortic valve dysfunction (range 5.0% to 26.3%) and 3.1% for mitral regurgitation of mild severity or greater (Loke, 2002; Sachdev, 2002).

In 1981, a report was published describing 2 patients who developed pulmonary hypertension while taking fenfluramine (Douglas, 1981). Additional rare cases, some of which severe or even fatal, were reported subsequently (McMurray, 1986; Pouwels, 1990).

Although QT prolongation is not a known effect of fenfluramine, no thorough QT study has been conducted thus far and no definitive data are therefore available. In a self-controlled, retrospective, observational crossover study in almost 60,000 patients, Iribarren (2013) examined the intra-individual change in log-linear regression-corrected QT for 90 drugs while adjusting for age, gender, race/ethnicity, comorbid conditions, number of ECGs, and time between pre-ECG and post-ECG. In this retrospective analysis of outpatient clinic patients which included 23 users of fenfluramine, a modest QT prolongation was observed with fenfluramine, at doses that were higher than those proposed for DS, with a point estimate of 15.3 milliseconds (95% CI 3.8, 26.7 milliseconds).

The current study reports on low doses of fenfluramine (30 mg/day or less) administered for up to 16 weeks. Two, mirrored studies of ZX008 in children and young adults with Dravet syndrome (ZX008-1501 and ZX008-1502) are being conducted concurrently; ZX008-1501 is being conducted in 30 sites in North America and ZX008-1502 is being conducted in 30 sites in Europe and Australia. These studies include evaluations of cardiac safety; echocardiograms for cardiac valve assessments and measures pulmonary arterial hypertension (PAH) and 12-lead electrocardiograms for the assessment of cardiac intervals, including the QT interval.

The first 119 subjects randomized between these two studies (hereinafter referred to as "Study 1") are the focus of the analysis described in this document.

This Statistical Analysis Plan (SAP) for Cardiovascular Endpoints outlines the planned analyses to support the assessment of electrocardiographic (ECG) and echocardiographic data in the Study 1 clinical study report. The planned analyses identified in this SAP may be included in regulatory submissions, and exploratory analyses not defined in this SAP may be performed to support a more thorough understanding of the safety data. All post-hoc or unplanned analyses performed not identified in this SAP will be documented.

Documents used to develop this SAP are:

- Study Protocol ZX008-1501 (version 3.0, 12 October 2016).
- Study Protocol ZX008-1502 (version 2.0, 31 October 2016).
- Study 1 Statistical Analysis Plan (version 2.0 10 August 2017).
- CAMI 7 12-Lead Analysis Plan for use with Eli 150c (Inventive Health/Zogenix) (Version 1.0 11 January 2016).
- ZX008 Investigational Brochure (version 5.0 28 April 2017).

2 Study Design and Cardiovascular Analysis Objectives

2.1 General Design and Plan

Study 1 contains pooled data from two studies, both are multicenter, randomized, double-blind, parallel group, placebo controlled trials of two fixed doses of ZX008 (Fenfluramine Hydrochloride) oral solution as adjunctive therapy in children and young adults with Dravet syndrome.

Electrocardiograms (ECGs) and echocardiograms (ECHOs) are being analyzed by Biomedical Systems (St. Louis, MO). All other study results for these subjects (demographics, efficacy, safety, PKw) will be presented in the Clinical Study Report for ZX008-Study 1.

Each subject is assigned to one of 2 treatments (0.2 mg/kg or 0.8 mg/kg) or placebo groups.

Treatments were assigned on a 1:1:1 basis.

All ECGs were reviewed and interpreted by a board-certified cardiologist.

Echocardiograms were reviewed by two, board-certified cardiologists. In the case of a discrepancy between the readers, the echocardiogram was sent to an adjudicator who chose which of the two readers was correct.

2.2 Objectives

The primary objective of Study 1 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). Safety endpoints of the study include the assessment for cardiac toxicity as demonstrated by ECG and ECHO.

2.2.1 Cardiovascular Safety Objectives

The primary cardiovascular safety objective of this analysis is to evaluate the effect of ZX008 on the heart as demonstrated by both the 12-lead ECG and ECHO.

Variables included in the analysis are listed below. These will be compared between Placebo and the 0.2 mg/kg and 0.8 mg/kg groups independently.

2.3 Endpoints

2.3.1 ECG

The change from baseline will be calculated and compared between placebo and the two dosing groups (0.2 mg/kg and 0.8 mg/kg) for the primary and secondary endpoints for each of the variables and subgroups listed.

2.3.1.1 Primary Endpoints

The primary endpoint will be the mean change between measurements of QT interval corrected using Fridericia's formula (QTcF) for ZX008 and placebo after

baseline adjustment, (ΔΔQTcF), calculating the upper bound of the one-sided 95% confidence interval.

2.3.1.2 Secondary Endpoints

The secondary endpoints that will be presented by dose and subgroups are:

- QRS duration
- PR interval measurements
- Heart rate
- Categorical analyses for each variable and subgroup listed below:
  - QTcF (number and percentage of subjects, by dose)

Age	Gender	Values
0 to < 12 years	Males and Females	< 320 ms
		≥ 320 ms to ≤ 450 ms
		> 450 ms to ≤480 ms
		> 480 ms
12 to 18 years	Males and Females	< 320 ms
	Males	≥ 320 ms to ≤ 450 ms
	Males	> 450 ms to 500 ms
	Females	≥ 320 ms to ≤ 470 ms
	Females	> 470 to ms ≤ 500 ms
	Males and Females	> 500 ms

- F

  or all ages QTcF changes from baseline (number and percentage of subjects, by dose)
  - ≤ 30 ms
  - > 30 ms to ≤ 60 ms
  - > 60 ms

- QRS (number and percentage of subjects, by dose)

Age	Gender	Values
2 to < 6 years	Males and Females	≤ 90 ms
		> 90 ms to ≤100 ms
		> 100 ms
6 to < 12 years	Males and Females	≤ 100 ms
		> 100 ms to ≤ 110 ms
		> 110 ms
12 to 17 years	Males and Females	≤ 110 ms
		> 110 ms to ≤ 120 ms
		> 120 ms
18 years	Males and Females	≤ 120 ms
		> 120 ms

- PR (number and percentage of subjects, by dose)

Age	Gender	Values
2 to < 6 years	Males and Females	≤ 90 ms
		> 90 ms to ≤ 150 ms
		> 150 ms
6 to < 12 years	Males and Females	≤ 100 ms
		> 100 ms to ≤ 170 ms
		> 170 ms
12 to 17 years	Males and Females	≤ 110 ms
		> 110 ms to ≤ 180 ms
		> 180 ms
18 years	Males and Females	≤ 120 ms
		> 120 ms to ≤ 220ms
		> 220 ms

- Heart rate (number and percentage of subjects, by dose)

Age	Gender	Values
2 to < 6 years	Males and Females	< 80 bpm
		≥ 80 bpm to ≤140 bpm
		> 140 bpm to ≤ 180 bpm
		> 180 bpm
		Increase or decrease from baseline >10 bpm
		Increase or decrease from baseline > 20 bpm
6 to < 12 years	Males and Females	< 60 bpm
		≥ 60 bpm to ≤120 bpm
		> 120 bpm to ≤ 150 bpm
		> 150 bpm
		Increase or decrease from baseline >10 bpm
		Increase or decrease from baseline > 20 bpm
12 to 18 years	Males and Females	< 50 bpm
		≥ 50 bpm to ≤100 bpm
		> 100 bpm to ≤ 150 bpm
		> 150 bpm
		Increase or decrease from baseline >10 bpm
		Increase or decrease from baseline > 20 bpm

- Overall characterization of normal and abnormal ECGs and the number and percentage of subjects with normal and abnormal ECGs. ECGs will be characterized as Normal, Abnormal Clinically Insignificant (ACI), or

Abnormal Potentially Clinically Significant (APCS). The number and percentage of ECGs within each category will be calculated by dose.

- Number and percentage of subjects that develop abnormalities of repolarization on treatment, as manifest by new ST and T wave abnormalities. The number and percentage of ECGs within each category will be calculated by dose.

Analysis for specific arrhythmias: Torsade de Pointes (TdP), ventricular tachycardia/fibrillation, atrial fibrillation/flutter, supraventricular tachycardia, etc., including associations between specific ECG findings and selected clinical adverse events of interest will be explored as appropriate (events that may signal pro-arrhythmia: syncope, palpitations, dizziness, tachycardia, etc.). Shift tables will be constructed for arrhythmias.

2.3.1.3 Listing for Abnormalities

Listings for ECG abnormalities by dosing, subject, and time-point will be provided for the following:

- Heart Rates
- PR-Interval
- QRS Duration
- QT-Interval
- First degree AV-Block
- Second degree AV-Block (Type 1)
- Second degree AV-Block (Type 2)
- Third-degree (complete) AV-Block

2.3.2 Echocardiograms

2.3.2.1 Primary Endpoint

The primary endpoint for the echocardiographic analysis is the change from baseline in the regurgitation score for the mitral and aortic valves.

2.3.2.2 Secondary Endpoints

Secondary endpoints are:

- Tricuspid valve regurgitation > Mild
- Pulmonic valve regurgitation > Mild
- Right Ventricular Outflow Tract Acceleration Time (RVOT)
- Pulmonary Artery Systolic Pressure (PASP)
- Pulmonic Valve Peak Regurgitation Jet Velocity (PVPR)

2.3.2.3 Heat Maps

Heat maps will be constructed for all valve scores.

2.4 Study Population

Male and female subjects, aged 2 to 18 years of age with a medical history and clinical diagnosis of Dravet syndrome who meet other eligibility criteria could be enrolled in the study. This section includes the inclusion and exclusion criteria related to cardiac safety.

2.4.1 Inclusion Criteria Related to Cardiac Safety

No inclusion criteria were related to cardiac safety.

2.4.2 Exclusion Criteria Related to Cardiac Safety

Subjects must not meet any of the following criteria to be eligible for study participation:

- Subject has Pulmonary Arterial Hypertension (PAH)
- Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke.
- Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoaminoxidase 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. (Note: Short term medication requirements will be handled on a per case basis by the Medical Monitor.)
- 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.

2.4.3 Sample Size

No formal sample size calculations were conducted related to cardiac safety for Study 1. The first 119 subjects that received study drug between ZX008-1501 and ZX008-1502 comprise Study 1.

2.5 Randomization and Blinding

Each subject was randomized in a 1:1:1 fashion and receive one of the following treatments:

A. 0.2 mg/kg/day ZX008

B. 0.8 mg/kg/day (up to 30 mg/day) ZX008

C. Placebo

Neither the subjects nor the investigator knew which treatment is being administered.

3 Cardiac Safety Data Collection and Analysis

3.1 ECG Assessment

3.1.1 Equipment

Twelve-Lead Electrocardiograms were collected on a Mortara ELI-150c ECG machine (Milwaukee, WI) located at each clinical site.

3.1.2 Transfer of ECGs

Electrocardiograms were digitally transferred to Biomedical Systems for analysis.

3.1.3 Collection of ECGs

The clinical ECG database will be derived from 12-lead ECGs collected from the ELI-150c ECG machines.

Single, 12-lead ECGs were collected at Screening, Baseline (Visit 3), Week 6 (Visit 8), and Week 14 (Visit 12). ECGs were collected after the subjects had been in supine position resting for ≥5 minutes.

The time of the ECG was not controlled.

3.1.4 Definition of Baseline

The baseline for this study will be the data collected from the ECG taken at Baseline (Visit 3).

3.1.5 Variables Measured

At the central laboratory, using CAMI software (or equivalent), the cardiac technician will annotate the Global Superimposed Median Beat (GSMB).

The following variables will be measured or calculated on each ECG:

- QRS duration
- PR interval
- Heart rate (10 second average)
- QT
    - The QT interval will be measured from the earliest detection of depolarization in any lead (beginning of the Q or R wave) to the latest detection of repolarization in any lead (end of the T-wave).

- QTcF

The RR interval will be reported, from which the corrected QT interval (QTc) using Fridericia's formula (QTcF) will be calculated.

Fridericia's correction: $QTcF = \frac{QT}{RR^{1/3}}$

where QT, RR, and QTcF are expressed in seconds.

For convenience, QT, RR, PR, QRS, and QTcF will be shown in milliseconds (ms) in the tables, figures and listings.

3.1.6 Clinical Analysis of ECGs

The over-reading cardiologist will give a clinical interpretation for each ECG at each time point. These will be presented in the data listing provided at the end of the study. Each ECG will be classified as Normal (N), Abnormal Clinically Insignificant (ACI), or Abnormal Potentially Clinically Significant (APCS).

3.1.7 Non-Digital ECG Evaluation

Data not acquired using the ECG equipment provided by Biomedical Systems will not be eligible for centralized reading, nor will it be included in the database.

3.2 Echocardiographic Analysis

3.2.1 Equipment

Site-owned equipment was used for the collection of echocardiograms.

Prior to being qualified for subject enrollment, all echocardiographers were required to participate in a WebEx PowerPoint training presentation and transferred test data to BMS. The WebEx session consisted of reviewing protocol specific views, study related forms and the process of uploading the images through web portal.

Each echocardiographer was required to submit a certification ECHO. The certification ECHO was performed on a non-study participant. The participating ECHO facility was informed during the training session that they would not be able to perform ECHOs on true study subjects until they received a "passed" Certification ECHO Evaluation Form.

3.2.2 Transfer of Echocardiograms

Electrocardiograms were either digitally transferred or copied to CD and sent via courier to BMS for analysis.

3.2.3 Collection of Echocardiograms

ECHOs were taken at Screening, Week 6 (Visit 8), and Week 14 (Visit 12). For each ECHO, cardiac technicians check to make sure the Nyquist Limit (color scale) was set between 60 cm/s and 80 cm/s. All sonographers at the study sites submitted a

certification ECHO before study ECHOs were obtained.

The time of the ECHO was not controlled.

3.2.4 Definition of Baseline

The baseline for this study will be the data collected from the ECHO taken at Screening.

3.2.5 Variables Measured

Echocardiograms were evaluated by two cardiologists using DigiView software. Details of the assessment and adjudication process are available in the ECHO operations manual for these studies.

In addition to assessing each valve (Mitral, Aortic, Tricuspid, and Pulmonary) for regurgitation, the following variables were measured or calculated on each ECHO:

- Right Ventricular Outflow Tract Acceleration Tim (RVOT)
- Pulmonary Artery Systolic Pressure (PASP)
- Pulmonic Valve Peak Regurgitation Jet Velocity (PVPR)

3.2.6 Clinical Analysis of ECHOs

Each ECHO was read, independently by two physicians. A third physician was assigned as an adjudicator. The adjudicator read the ECHO if the any of the following discrepancies occurred between the first and second reader:

- Aortic valve findings were not identical
- Mitral valve findings were not identical
- LVFS difference between the two physicians was >5%
- LVEF difference between the two physicians was >10%
- PASP difference between the two physicians was >10 mmHg
- Clinical significance between the two readers was not identical

The adjudicator chose which of the two readings was the final reading.

3.2.7 Alert Criteria

Echocardiographic alert criteria included:

- Valve regurgitation (aortic or mitral)
- ≥ moderate valve regurgitation (tricuspid or pulmonic)
- Mean mitral valve gradient ≥ 4 mmHg
- Mean aortic valve gradient ≥ 15 mmHg

- Mean tricuspid valve gradient ≥ 4 mmHg
- Peak pulmonic valve gradient ≥ 21 mmHg
- Tricuspid regurgitation jet velocity > 2.8 meters/sec with or without the findings OR
- One of the following findings in the absence of being able to measure tricuspid regurgitation jet velocity:
    - Change in right ventricle/left ventricle basal diameter ratio > 1.0
    - Right ventricular outflow tract flow acceleration time < 100 msec
    - Dilation of the inferior cava vein (diameter > 21mm and <50% inspiratory collapse) and/or right atrial dilatation
    - Change in the geometry of the interventricular septum in systole (flattening) with left ventricular eccentricity index >1.1 in systole and/or in diastole
    - Early diastolic pulmonary regurgitation velocity > 2.2 m/sec
    - Tricuspid Annular Plane Systolic Excursion below 18 mm or below Z-score – 2

4 Statistical Analysis

The statistical analyses of the cardiac safety data is designed to assess the potential toxicity of ZX008 when administered for up to 14 weeks as adjunctive treatment for children and young adults with Dravet syndrome.

4.1 General Principles and Considerations

This section describes the algorithms and conventions that will generally apply to program analyses and to the formatting of the data, as required to perform the proposed summary tabulations and to create the individual subject data listings. Unless otherwise indicated, these specifications will apply to all analyses. For details on the tables and figures that will be created, please refer to Section 5, Tables, Figures, and Listings.

The statistical analysis will be reported using summary tables, figures, and data listings.

ECG and ECHO variables at each time point will be obtained. Changes from baseline will be compared for the 0.2 and 0.8 mg/kg/day treatment groups to placebo.

Continuous variables will be summarized using descriptive statistics (i.e., total number, mean, standard deviation [SD], minimum, maximum, and 95% CI). Results will be presented to one or two decimal places for means and SD, as appropriate.

Qualitative variables will be presented as category counts and percentages. Percentages will be presented to one decimal place.

All dates will be displayed in DDMMMYYYY format (e.g.,15DEC2012).

All analyses will be carried out using SAS® Version 9.2 or higher.

4.2 Analysis Set

ECG and ECHO data will be analyzed using a modified Intention-to-Treat dataset, including all randomized subjects who received at least one dose of study medication.

As there are few subjects per site, no comparisons between sites will be conducted.

4.2.1 Handling of Missing Data

All data available will be used for the analysis. Missing data points will not exclude the rest of the subject's data from analysis, and missing data will not be imputed.

4.3 Interim Analysis

No interim analysis is scheduled for this trial.

4.4 Multiplicity Adjustments

No adjustments for multiplicity will be made for the primary cardiovascular endpoint.

4.5 Primary Analyses

4.5.1 Electrocardiogram

The primary ECG objective is to evaluate the effect of ZX008 0.8 mg/kg/day (max 30 mg/day) on QTcF.

The primary analysis of the QTcF is the mean baseline-adjusted difference between treatment and placebo and will be performed using an analysis of variance (ANOVA) for each post-dose time point. The ANOVA model will include a fixed effect for treatment. The upper bound of the one-sided 95% CI (or, equivalently, two-sided 90% CI) of the mean baseline-adjusted difference between treatment and placebo QTcF (ΔΔQTcF) will be calculated from the ANOVA for each time point.

The general formula to calculate the ΔΔQTcF at the *i*th timepoint is:

> Mean ΔΔQTcF*i* = Mean ΔQTcF*i*for the active group - Mean ΔQTcF*i*for the placebo group, based on the ANOVA model, where *i* = at *i*th timepoint and ΔQTcF*ti* =QTcF*ti*on Day 1 –QtcF*ti* at Baseline (i.e., Day -1), where *ti* = at *i*thtime point for subject t

4.5.2 Echocardiogram

The primary ECHO objective is to evaluate the effect of ZX008 0.8 mg/kg/day (max 30 mg/day) on the mitral and aortic valves.

The primary analysis of the mitral and aortic valves is the change from baseline in regurgitation category between treatment and placebo and will be performed using a Chi-Square test.

4.6 Secondary Analyses

Analyses conducted with 0.8 mg/kg/day (max 30 mg/day) ZX008 will be conducted with 0.2 mg/kg/day ZX008. Central tendency analyses will be conducted to include per-visit data and changes from baseline and placebo for the ECG and ECHO values for all subjects. The variables for analysis are listed in sections 2.3.1.2 and 2.3.2.2.

4.7 Additional Analysis

Additional analysis may be used, as appropriate.

4.8 Categorical Analysis

Categorical data will be reported as both numbers and percentages and will include changes from baseline in both ECG and ECHO variables.

5 Tables, Figures, and Listings

A set of Tables, Figures, and Listings is attached.

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ZX008 Investigator's Brochure. Edition 5.0. 28 April 2017. Zogenix International Limited.

ZX008-1501: 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. 31 October 2016 (Protocol Amendment 3.0).

ZX008-1502: 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. 31 October 2016 (Protocol Amendment 2.0).

16.1.9 Documentation of Statistical Methods

The document listed below is provided in this section.

Statistical Analysis Plan (Study ZX008-1501 & Study ZX008-1502) dated 21-May-2020

Statistical Analysis Plan (Study ZX008-1501 & Study ZX008-1502) for Cardiovascular Endpoints dated 09-June-2020

Statistical Analysis Plan for Interventional Studies

Sponsor Name: Zogenix International Limited

Protocol Number: ZX008 Study 2 (ZX008-1501 and ZX008-1502)

Protocol 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

Protocol Version and Date: ZX008-1501: 02-Nov-2015 Version 1.3
18-Dec-2015 (Amendment 1.0)
18-Jan-2016 (Amendment 2.0)
31-Oct-2016 (Amendment 3.0)
ZX008-1502: 30-Oct-2015 Version 1.0
11-Jan-2016 (Amendment 1.0)
31-Oct-2016 (Amendment 2.0)
07-Feb-2019 (Amendment 2.4.3)

Syneos Health Project Code: 7012988

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Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
Draft 0.1	16-Apr-2020	[redacted]	Initial Release Version
Draft 0.2	30-Apr-2020	[redacted]	Per Zogenix review
Final 1.0	19-May-2020	[redacted]	SAP finalization
Final 1.0	21-May-2020	[redacted]	SAP finalization

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

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Zogenix International Limited Approval

[redacted]

[redacted]

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Abbreviation	Description
AE	Adverse Event
AED	Antiepileptic Drug
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
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
CDISC	Clinical Data Interchange Standards Consortium
CGI	Clinical Global Impression
CI	Confidence Interval
CRF	Case Report Form
CMH	Cochran–Mantel–Haenszel Test
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
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-related Quality of Life
ET	Early Termination
FDA	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HR	Heart Rate
ICH	International Conference on Harmonization
IDSMC	Independent Data Safety Monitoring Committee

Abbreviation	Description
IMP	Investigational Medicinal Product
IPCAB	International Pediatric Cardiology Advisory Board
IVR	Interactive Voice Randomization
IWR	Interactive Web Response (System)
kg	kilogram
kg/m^2	kilogram per meter square
MCSF	Mean Convulsive Seizure Frequency
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg/day	milligram per kilogram per day
min	minute(s)
mITT	modified Intent-to-Treat
mL	milliliter
MMRM	Mixed Effects Model for Repeated Measures
msec	millisecond
PedsQL	Pediatric Quality of Life Inventory
PD	Pharmacodynamics
PDCO	Pediatric Committee of the European Medicines Agency
PK	Pharmacokinetic
PP	Per Protocol
QoL	Quality of Life
QOLCE	Quality of Life in Childhood Epilepsy Quality of Life
QTcF	corrected QT interval using Fredericia method
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SMEI	Severe Myoclonic Epilepsy Of Infancy
SOC	System Organ Class

Abbreviation	Description
T+M	Titration plus Maintenance Periods (14 wks, randomized treatment period)
M	Maintenance Period
TEAE	Treatment Emergent Adverse Event
THC	Tetrahydrocannabinol
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization Drug Dictionary
ZX008	Proprietary name for Fenfluramine Hydrochloride

SCOPE

Zogenix is conducting two identical Phase 3 studies of ZX008, Study ZX008-1501 (Study 1501) and Study ZX008-1502 (Study 1502). Study 1501 is being conducted in the United States and Canada; Study 1502 is being conducted in Europe, Australia and Japan. Approximately 120 subjects with Dravet syndrome, a rare form of pediatric epilepsy, are planned for randomization into each study in three treatment groups: 0.2 mg/kg/day ZX008, 0.8 mg/kg/day ZX008 and placebo (n=40/group). Due to slow enrollment into both trials, the databases for the two trials were combined and the first 120 subjects randomized were analyzed and reported as Study 1. Additional randomized subjects (over N=120) are intended to be reported as Study 2, and are covered in this Statistical Analysis Plan (SAP). Primary and key secondary analyses in the Study 2 SAP remain as stated in the protocols and as described in the Study 2 draft SAP with some changes delineated in this SAP based on FDA feedback.

1. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives, and allow for review by regulatory authorities according to stated guidelines.

This Statistical Analysis Plan (SAP) is based on the protocols for Study ZX008-1501 version 3.0 dated Oct 31, 2016, and Study ZX008-1502 version 2.4.3 dated Feb 7, 2019. The two protocols are identical in design, conduct, and randomization scheme; the latest amendment for Study 1502 added Japan.

1.1. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures and listings with the exception of pharmacokinetics (PK), electrocardiogram (ECG), and echocardiogram (ECHO).

There are separate analysis plans for PK and for electrocardiogram (ECG) and echocardiogram (ECHO) data .

ERT (formerly BioMedical Systems), will provide analyses of ECG and ECHO data.

1.2. Timings of Analyses

The primary analysis of safety and efficacy is planned after all subjects complete the final study visit or terminate early from the study, and after all databases are locked.

2. Study Objectives

2.1. Primary Objective

The primary objective of Study 2 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. Secondary Objective(s)

The key secondary objectives of Study 2 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 ≥50% reduction from baseline in convulsive seizure frequency.
    - The longest convulsive seizure-free interval.

Additional Secondary Objectives:

- 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 ≥25%, or ≥75%, or 100%, or near seizure-free (ie, at most 1 convulsive seizure) 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.
    - The change from baseline in the Pediatric Quality of Life Inventory™ (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 Hospital Anxiety and Depression Scale (HADS).

The safety objective of the Study 2 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 bodyweight. Cognitive function will be assessed using age-appropriate versions of the Brief Rating Inventory of Executive Function (BRIEF).

Pharmacokinetic Objective:

- The pharmacokinetic (PK) objective of Study 2 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.

Exploratory Objective

The exploratory objective of the Study 2 is:

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

2.3. Brief Description

Both Study 1501 and Study 1502 are multicenter, double-blind, parallel-group, placebo-controlled studies designed to assess the efficacy, safety, and PK of ZX008 when used as adjunctive therapy in pediatric and young adult subjects with Dravet syndrome. Study 1501 was conducted at approximately 30 study sites in North America; Study 1502 was conducted at approximately 30 study sites in Europe, Australia, and Japan. For Study 1502 Japan was added in 2019 whereas Europe and Australia started in 2015. Approximately 36 sites will contribute randomized subjects to Study 1502.

The expected study period of 22 weeks comprises a Baseline period (6 weeks), a Treatment period (14 weeks) (2 weeks titration + 12 weeks maintenance), and a Post Dosing visit 2 weeks after study completion or early termination.

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. There will be cardiac safety follow-up of 3 to 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. Subjects from France, Germany and the Netherlands will have a cardiac safety follow-up visit approximately 24 months after the last dose of active study medication. Follow-up safety visit results will be reported separately.

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, with the target of 25% of subjects in each age group. Subjects will be assigned a randomization number by the 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. The randomization scheme and block size for Studies 1501 and 1502 are the same, so combination of the data from the two studies will not skew the intended randomization into the three treatment groups.

Due to slow enrollment, Studies 1501 and 1502 were merged into a single dataset for analysis and reporting. The first 119 subjects randomized comprised Study 1, which was reported in September 2017. This analysis enabled an earlier determination of the benefit-risk profile of ZX008, to minimize the total subject exposures should the risk-benefit profile not be positive. The subsequent approximately 120 subjects to be randomized, comprise Study 2. Study 2 represents the cohort of subjects in Studies 1501 and 1502 whose data were not included in Study 1.

Study 1501 and Study 1502 are being conducted in parallel with each study independently assigning treatments using randomized permuted blocks; thus, combining subjects from the two identically designed studies meant that 2 sets of randomized blocks were used, which had approximately the same effect as doubling the block size in a single study. Combining the first 120 randomized subjects from Study 1501 and Study 1502 to create Study 1 and Study 2 preserves the balance among the 3 treatment groups in each of Study 1 and Study 2, yielding approximately 40 subjects per arm, the number required to maintain full statistical power.

After the last of the subjects in Study 2 has either discontinued or completed treatment, the database will be locked for those subjects and Study 2 will be reported as per this SAP.

2.4. Subject Selection

The study population will be selected on the basis of the inclusion and exclusion criteria described in the protocol.

2.5. Determination of Sample Size

The sample sizes for Zogenix Studies 1501 and 1502 were calculated based on the results of two trials with stiripentol reported in the European Public Assessment Report (EPAR) for stiripentol (EMA, 2007). The stiripentol 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 Protocols 1501 and 1502 that compares 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 yielded a requirement for an additional 35 subjects in the 0.2 mg/kg/day ZX008 group. The total sample size for each study was therefore set at 105 subjects.

In December 2016 results from a double-blind, placebo-controlled Phase 3 study with Epidiolex® (cannabidiol) to treat seizures in Dravet syndrome were presented at the American Epilepsy Society Meeting (http://ir.gwpharm.com/events.cfm). In the Epidiolex study, active drug reduced seizures by 39% compared to a reduction of 13% in the placebo. Review of the data suggested that the standard deviation was relatively large, likely above 50% in both treatment groups. In consideration of this new data, the sample size was re-estimated for the ZX008 studies to assume a SD of 55%, higher than the previous estimate of 50%. Other assumptions in the sample size calculation remained unchanged. A sample size of approximately 120 subjects (40 per arm) affords 90% power to detect a difference in mean change from baseline of 40 percentage points with 55% SD. Considering the variability seen in the STILCO and Epidiolex trials, the sample size for Study 1 and Study 2 is set at 120 subjects, 40 per treatment arm. Note that the change in assumed SD was based entirely on data from external trials. Efficacy data from both Study 1501 and 1502 are still blinded and were not used in re-estimating the required sample size.

2.6. Treatment Assignment & Blinding

Subjects in Study 2 were originally in either Study 1501 or Study 1502. 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 was stratified by age (<6 years, ≥6 years) to ensure balance across treatment arms, with

a target of ≥25% of subjects in each age group. Subjects were assigned a randomization number by IWR system upon confirmation that the subject qualified for enrollment in the Titration Period. Once a randomization number was assigned to a subject, the site recorded the subject's initials and identification number on the corresponding study drug bottles.

Each bottle contained the assigned treatment (ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day, or placebo). ZX008 and placebo were identical, thus rendering the study drug and placebo indistinguishable. The blinding scheme instituted for this study ensured that the volume of study medication taken could not be associated with the dose group, thus unblinding the study. This was 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 IWR system instructed site personnel to the volume of oral solution to be administered based on that subject's weight. (Dose was to 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) were blinded to the treatment allocation and to the concentration of ZX008 oral solution.

Prior to database lock for Study 1 an unblinding plan was implemented. The purpose of unblinding plan was to provide specific information and guidance to the Clinical Development Team, Clinical Operations Team, Biostatistics, Project Management, and other functions regarding plans for unblinding key team members for analysis of Study 1 top-line data and final Tables, Listings, and Figures (TLFs). 'Unblinding' is defined as having access to subject-level data (i.e., subject data listings or the randomization codes) that provides information regarding randomized dose group, treatment effect, and safety. Access to aggregated data (ie, group-level tables and figures) does not constitute 'unblinding' and for the purposes of data cleaning and database lock, these individuals were still considered 'blinded'.

Personnel from the sponsor or any designee who became unblinded for the purposes of data cleaning and database lock for Study 1 did not participate in any decision-making regarding subjects' data for Study 2 to avoid any real or apparent bias in such decisions. Study 2 was to be completed by a blinded study team with personnel distinct from the unblinded team that worked on Study 1.

2.7. Administration of Study Medication

ZX008 is supplied as an oral solution in concentrations of 1.25, 2.5, and 5 mg/mL. Subjects were 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. Placebo 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.

Study medication was administered twice a day (BID) in equally divided doses with food.

- Treatment ARM A: ZX008 0.2 mg/kg/day
- Treatment ARM B: ZX008 0.8 mg/kg/day
- Treatment ARM C: Placebo

Treatment Periods:

Titration Period:
Study medication was administered as equal doses BID in the morning and in the evening approximately 12 hours apart, with food. Each dose should have been separated by a minimum of 8 hours and a

maximum of 12 hours. A missed dose of study medication was to be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given.

Administration of the Investigational Medicinal Product (IMP) was based on the randomized dose and subject's weight at Visit 3 (Day -1). At Visit 8 (Day 43), if the subject's weight changed ±25% of the weight at Day-1, the IMP dose was recalculated. Subjects were dosed using the oral dosing syringe provided.

In order to maintain the blind across all dose groups and allow step titration to the high dose, the dose for each subject was titrated starting with a dose of ZX008 0.2 mg/kg/day (or placebo equivalent) BID. After 4 days at this dose level (Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group increased their dose to 0.4 mg/kg/day while doses in the other two groups remained constant. On Day 9, the dose for the 0.8 mg/kg/day group increased to the target dose. The titration was expected to take a total of 14 days (Table 1). A new bottle of IMP was started by the subject at each level of the titration step.

Table 1: 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.			

Maintenance Period:

After completion of the Titration Period, subjects entered the Maintenance Period and continued to receive the randomized dose of ZX008 or placebo and be treated for an additional 12 weeks. Study medication continued to be administered BID in the morning and in the evening, approximately 12 hours apart, with food. Each dose was to be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may have been taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose was not to be given.

Taper Period:

Subjects who complete the Maintenance Period and were not continuing into the open-label extension study and subjects who discontinued from the study early were to be tapered off from study medication. Study medication was administered as equal doses BID in the morning and in the evening approximately 12 hours apart, with food. Each dose should have been separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may have been taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given. IMP was administered using the oral dosing syringe provided.

In order to maintain the blind across all dose groups, all subjects who did not continue into the open-extension study participated 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 decreased to a dose of ZX008 0.4 mg/kg/day BID (maximum 30mg/day). After 4 days at this dose level (Day 5), subjects randomized to the ZX008 0.8 mg/kg/day group decreased their dose to 0.2 mg/kg/day. Subjects in the ZX008 0.2 mg/kg/day group decreased their dose to placebo on the first day of tapering while doses in the placebo group remained constant throughout the tapering procedure. On Day 9, all subjects stopped taking study medication. The taper was expected to take a total of 8 days (Table 2). A new bottle of IMP was started by the subject at each level of the taper step.

Table 2. 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.		

Transition Period:

Subjects who completed the Maintenance Period and were continuing into the open-label extension study were to be transitioned from double-blind study medication to open-label ZX008 (Table 3). Study medication was administered as equal doses BID in the morning and in the evening approximately 12 hours apart, with food. Each dose should have been separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may have been taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given. Study medication was administered using the oral dosing syringe provided.

All subjects entering the open-label extension study were 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 IWR system assigned two bottles of IMP to the subject, one for each step in the transition. A new bottle of IMP was started by the subject at each level of the transition step.

Table 3. 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 increased 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 continued 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 decreased 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 decreased their dose to 0.2 mg/kg/day. Subjects were to report to the clinic on Day 15 for enrollment into the open-label extension study.

Data from the Taper or Transition period will not be included towards the planned efficacy endpoints except where specified, but will be included in the safety analyses.

2.8. Study Procedures and Flowchart

The full list and timing of study procedures is provided in Table 4.

Table 4: Schedule of Assessments

	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Post-Dosing	Cardiac Follow-up
Study Assessments	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 to -41	-21	-1	1	4, 8	15	29	43	57	71	85	99	113	3-24 mo post dose
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													
Study Medication			D		R[i]	C/R/D	R	C/R/D	R	C/R/D	R	C/R/D[i]	C/R	
C-SSRS	X		X			X		X		X		X		

Table 4: Schedule of Assessment (Continued)

Study Assessments	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Post-Dosing	Cardiac Follow-up
				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 to -41**	**-21**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**3-24 mo post dose**
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										
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.
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 if warranted 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
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.

The targeted study day and allowable windows for visits in are reproduced from the protocol below. Early termination visits will be mapped to a visit based on these windows.

Table 5. 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

3. Endpoints

3.1. Primary Efficacy Endpoint

The change from baseline in the mean convulsive seizure frequency (MCSF) in combined Titration and Maintenance Periods (T+M) in the ZX008 0.8 mg/kg/day group compared to the placebo group.

The primary endpoint will be assessed using a parametric analysis of covariance (ANCOVA). MCSF will be log-trnasformed prior to analysis. If the assumptions of the parametric ANCOVA model are not met, the primary endpoint will be assessed using a nonparametric ANCOVA where MCSF is rank-transformed prior to analysis.

4. Key Secondary Efficacy Endpoints

The key secondary endpoints of Study 2 are:

- Change from baseline in in the mean convulsive seizure frequency (MCSF) in T+M in the ZX008 0.2 mg/kg/day group compared to the placebo group.

  The change from baseline in MCSF for the ZX008 0.2 mg/kg/day group will be analyzed using the same methods as the primary analysis.

- ZX008 0.2 and 0.8 mg/kg/day dose groups compared independently versus placebo on the

  - The proportion of subjects who achieve a ≥50% reduction from baseline in convulsive seizure frequency.

    The proportion in each ZX008 treatment group will be compared independently to placebo using logistic regression analysis.

  - The longest convulsive seizure-free interval during T+M.

    Each ZX008 treatment groups will be compared to placebo on the longest interval using an independent Wilcoxon rank-sum test.

The additional secondary endpoints are:

ZX008 0.2 and 0.8 mg/kg/day dose groups compared independently versus placebo on the

- The number of convulsive seizure-free days.
- The proportion of subjects who achieve ≥25%, ≥75%, or 100% reductions from baseline in convulsive seizure frequency.
- The proportion of subjects with at most 1 (ie, ≤1 convulsive seizure) during T+M.
- 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.
- 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.
- The change from baseline in the Pediatric Quality of Life Inventory™ (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 Hospital Anxiety and Depression Scale (HADS).

4.1. 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

4.2. 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

4.3. Exploratory Endpoints

ZX008 0.2 mg/kg/day compared versus ZX008 0.8 mg/kg/day on primary, secondary, safety and PK endpoints mentioned above.

Exploratory Analyses due to Covid-19
Additional exploratory analyses may be conducted to determine the impact of Covid-19, including but not limited to, protocol deviations, missed visits and missing data, alternative data collection. Any exploratory analyses related to Covid-19 will be described in the Clinical Study Report.

5. Analysis Populations

5.1. Randomized / Enrolled Population

The Enrolled Population includes all subjects who signed the informed consent form. This population will be used to present overall study disposition data and the number of subjects in each study population.

The Randomized Population includes all subjects randomized to receive study treatment.

5.2. 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 group to which they were randomized.

5.3. 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 ZX008 0.8 mg/kg/day to placebo, as well as key secondary analyses, will be performed on the mITT Population.

5.4. Per Protocol (PP) Population

The PP Population includes all randomized subjects who receive at least one dose of ZX008 or placebo, complete at least 4 weeks of the Maintenance Period, and have no important protocol deviations that would have a significant impact on clinical outcome. Subjects will be analyzed according to the treatment group to which they were randomized. Protocol deviations will be reviewed and the list of deviations warranting exclusion from the PP Population will be finalized prior to study unblinding.

The primary and key secondary efficacy analyses will be repeated on the PP Population.

5.5. Protocol Deviations

Major protocol deviations will be summarized overall and by site based on the SAF population. Major protocol deviations are those that have the potential to impact subject safety and/or affect data integrity and/or the efficacy conclusions. Major protocol deviations will be grouped into categories and may include categories, including but not limited to:

- Violation of inclusion/exclusion criteria
- Violation of randomization inclusion criteria
- Non-compliance regarding intake of IMP
- Inappropriate intake of concomitant medication
- Subject not discontinued as per protocol
- Other non-compliance

Multiple deviations can occur in the same subject and thus a subject can be counted in more than 1 deviation category.

Major and minor protocol deviations will be presented in a subject data listing for the enrolled population, sorted by treatment, site, and subject.

Deviations will be reviewed prior to the database lock of Study 2 data to determine which deviations will be classified as leading to exclusion from the PP population.

6. General Aspects for Statistical Analysis

6.1. General Methods

All statistical analyses will be performed using SAS statistical software (Version 9.4 or later).

Study 2 summaries will be presented by treatment group (Placebo, ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day).

Continuous data will be summarized using descriptive statistics including means, standard deviations, medians, lower and upper quartiles, minimum and maximum values. Categorical variables will be summarized with frequencies and percentages. Confidence intervals will be calculated for key parameters or estimates as warranted.

Two-sided statistical significance testing ($\alpha = 0.05$) comparing each active treatment to placebo will be performed for the primary and secondary endpoints as described below, unless otherwise noted.

All relevant collected subject data will be included in listings. All subjects entered into the database will be included in data listings.

Unless otherwise specified in the subsequent sections, in the event of multiple assessments at a given planned time point, the latest collected value will be used for the summarization.

6.2. Key Definitions

Study Day: Study Day 1 is considered the day after Randomization Visit 3. Study day will be calculated relative to the Study Day 1. For any date on or after the Study 1, study day will be calculated as assessment date – Study Day 1 + 1. For any date prior to the Study 1, study day will be calculated as assessment date – Study Day 1. There will be no Study Day 0.

Baseline Value: Baseline period consists of 42 days immediately preceding Study Day 1. Any assessment performed during these 42 days preceding Study Day 1 will be considered for baseline assessment.

For the change in the frequency of convulsive seizures endpoint, baseline will include all data from the baseline period of 42 days immediately preceding Study Day 1. For all other endpoints, baseline is the last non-missing result from the Baseline period prior to Study Day 1.

Other Definitions:

Treatment completers are those subjects that are compliant with IMP at least 85% of dosing days and fulfill at least one of the following criteria:

- Subjects that did not discontinue from the trial prior to end of study visit at Day 99 ± 4 days (Visit 12).
- Subjects that complete the Treatment Period (T+M) starting from Study Day 1 through the protocol defined end of study visit at Day 99 ± 4 days (Visit 12).
- Subjects that enroll in the open label extension study.

6.3. Multiplicity Strategy and Testing Hierarchy

Multiplicity issues in the statistical inference in this study arise from two sources: (a) multiple treatment comparisons, and (b) multiple endpoints.

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.

All statistical analyses will be performed and results tabulated with test statistics, p-values, and/or 95% confidence intervals.

Formal statistical testing will be performed for 1 primary endpoint and 2 secondary endpoints, for the comparison of ZX008 0.8 mg/kg with Placebo, and between ZX008 0.2 mg/kg with Placebo. Hence there are 6 formal hypothesis tests: 1 primary hypothesis test and 5 secondary hypothesis tests. To preserve the overall Type 1 error rate at α=0.05, these tests will proceed as follows:

Step 1: The primary efficacy endpoint (mean convulsive seizure frequency per 28 days) will be formally tested first between the 0.8 mg/kg and Placebo group. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 2. Otherwise formal testing of the other hypotheses stops.

Step 2: The secondary efficacy endpoint, the proportion of subjects who achieve a ≥50% reduction from baseline in convulsive seizure frequency, will be compared between the 0.8 mg/kg and Placebo group. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 3. Otherwise formal testing of the other hypotheses stops.

Step 3: The endpoint, the longest convulsive seizure-free interval will be compared between 0.8 mg/kg and Placebo. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 4. Otherwise formal testing stops.

Step 4: The mean convulsive seizure frequency per 28 days will be formally tested first between the 0.2 mg/kg and Placebo group. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 5. Otherwise formal testing of the other hypotheses stops.

Step 5: The secondary efficacy endpoint, the proportion of subjects who achieve a ≥50% reduction from baseline in convulsive seizure frequency, will be compared between the 0.2 mg/kg and Placebo group. If the comparison is statistically significant at the α=0.05 (2-sided) level, hypothesis testing will proceed to Step 6. Otherwise formal testing of the other hypotheses stops.

Step 6: The endpoint, the longest convulsive seizure-free interval will be compared between 0.2 mg/kg and Placebo using a significance level of α=0.05 (2-sided).

6.4. Missing Data

Imputation for missing data is used in the sensitivity efficacy analyses.

Seizure Diaries:

Seizures are recorded in the Daily Seizure Diary (DSD). The End of Day Diary (EDD) provides Yes/No confirmation that seizures were experienced for a specific date or that the date was seizure free. The DSD was programmed to allow for up to 7 days of retrospective entry for daily seizures and to allow entry for EDD by 11:59 pm each day to confirm (Y/N) each day whether the day was seizure-free. Changes outside these parameters would therefore need to be made via the Data Clarification Request (DCR) process. Additionally, through a pre-specified process DCRs were used to categorize new seizures that

emerged during the treatment period. Specifically, new seizures were entered into the DSD as "Other" and after review of the seizure description by the Epilepsy Study Consortium, "Other" was updated to the appropriate clinical term via DCR.

DCR data were processed prior to applying the missing data rules described below:

- If no seizures are entered in the DSD and the EDD confirms seizure freedom, the number of seizures for that date is zero.
- If seizures are entered in the DSD and the EDD states seizure freedom, the seizures recorded for that date supersede the EDD stating seizure freedom.
- If no seizures are entered in the DSD and there is no response in the EDD, that day will be considered to have missing diary data.
- If no seizures are entered in the DSD and there is a Yes response in the EDD, that day will be considered to have missing diary data.

Based on analyses of the blinded, pre-lock database for Study 1, seizures clusters that were entered into the DSD without a number of seizures in the cluster had a value of 3 was imputed for the seizure count.

Missing Data Due to Dropouts:

The issue of missing data has gained much attention subsequent to the National Academy of Science Report on the Treatment and Handling of Missing Data (NAS Report, 2010). Within the context of the studies, missing data arise from two sources: intermittent missing assessments (such as missing diary data), and as a result of dropouts prior to the end of the titration + maintenance periods.

In Study 1, only 2 (out of the 119) subjects had more than 7 days of missing diary data while on treatment (before dropout). The rates of dropout in the pivotal trials was 7.56% (9/119) in Study 1. Dropouts that are related to treatment response leave the possibility that the analysis of efficacy endpoints, which relies on assumptions of data being missing at random (MAR), may be violated. It is possible, though, that data may be missing not at random (MNAR). Differential dropouts leading to missing assessments may thus affect the inference on the primary endpoint.

The primary analysis method, in so far as it uses the convulsive seizure frequency averaged over the entire treatment period, in effect, assumes that a dropout would have followed the mean profile experienced up to that point in time when the subject dropped out from the study. Alternative, explicit, ways of addressing the issue of missing seizure data due to dropouts may be considered. (Kenward 2015)Two methods were chosen for minimal impact on variability of estimates as well as their simplicity.

It is assumed that the ***planned duration*** of T+M for Study 1 and Study 2 subjects is 14 weeks (98 days).

S1: Worst value substituted: In this analysis, for a subject who drops out of treatment, if the convulsive seizure frequency during T+M is lower than the baseline value, the baseline value will be substituted for the subject from the point of withdrawal to the end of the planned duration of T+M. However, if it is higher than the baseline, there will be no substitution. The CSF for the planned duration of T+M will then be computed as a weighted mean of the value before dropout, and the imputed value after dropout. The weights will be the proportion of planned duration of T+M before and after dropout. The statistical analysis (parametric ANCOVA with log CSF_{T+M} as response and log CSF_B as covariate, along with age group, treatment (2 factors: placebo, ZX008)) will then be performed on the resulting dataset. Treatment comparisons will be based on the least squares means and standard errors obtained from the ANCOVA.

S2: Intermediate Missing Day and Post-Discontinuation Imputation: Intermediate missing days should be imputed as the worse observed outcome for that patient if the patient was assigned to an active arm or zero seizures if the patient was assigned to placebo.

For patients who discontinued the study, the day of discontinuation should be imputed as the worse observed outcome if assigned to ZX008 and as zero counts if the patient was assigned to placebo. The remaining days should be imputed using the baseline seizure counts for all arms.

For cluster seizures that were reported as uncountable, the assigned number of seizures in the cluster is assigned as the worst cluster value for each individual subject in the active arm, and assigned as the mean baseline seizure count if the subject was assigned to placebo.

Handling of missing date information for AEs:

1. The term missing date refers to a completely missing date or to an incomplete date/partial date where parts are not available, e.g. missing month/day/year.
2. Missing start and end date will be imputed conservatively, i.e. missing values will be imputed in such a way that the duration of the AE is considered with the longest possible duration and such that, whenever the AE may potentially start after first IMP, the AE will be handled as a TEAE.
3. The missing start date and End date of AE will be imputed for the purpose of calculating treatment emergent status and assigning events to treatment periods using definitions given in the following table.

	Adverse event
Partial /Missing Start date	Missing day – If Adverse event start day is missing but month and year is present then Impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date. Missing day and month – If adverse event start day and month are both missing but year is present then impute 1st January unless year is the same as first dose date then impute first dose date. Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date. When imputing a start date, ensure that the new imputed date is sensible i.e. is prior to the end date of the AE.

	Adverse event
Partial /Missing End date	Missing day – If AE end day is missing but month and year are present then Impute the last day of the month unless month is same as month of last dose of study drug then impute last dose date. Missing day and month – If AE has missing day and month but year is present then impute 31st December unless year is the same as first dose date then impute last

	dose date. Completely Missing – need to look at whether the AE is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present (i.e. do not impute a date). If the AE has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is after the last dose date.

6.5. Visit Windows

The following rules will be used to window data into treatment periods for by treatment period tabulations. For all by-visit tabulations, the nominal visit as recorded on the CRF will be used.

Double Blind Treatment Period	The Double-Blind Treatment Period start date is the date of first treatment, Study Day 1 (ie, the day after V3). The Double-Blind Treatment Period end date is the last date the patient was on study treatment. The Double-Blind Treatment Period consists of 16 weeks from first treatment start date, which includes 2 weeks of Titration period, 12 weeks of Maintenance period and 2 weeks of Taper/Transition period; therefore the end date would be considered the date at Visit 13. For subjects who discontinue early from the study, the double-blind treatment period end date will be the date at the early termination visit (Visit 12).
Titration Period	The Titration Period covers the first 14 ± 4 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 Visit 6 (when the patient has reached their randomization dose). The Titration Period applies to all subjects including placebo recipients. If a subject withdraws from the study prior to treatment in the maintenance period, all safety assessments and events up to and including the date of study withdrawal will be tabulated in the titration period.
Maintenance Period	The Maintenance Period covers the 12 weeks following the end of the titration period. It begins on the date of Visit 6 + 1 day and extends through the end of study/early termination visit (Visit 12).
Titration + Maintenance Period (T+M)	The T+M period combines the Titration and Maintenance periods, beginning on the date of first treatment (Study Day 1) and extending to the end of study/end of treatment visit. The T+M period is considered the treatment period.
Taper/Transition Period	The Taper/Transition period consists of 2 weeks starting from end of study/early termination visit (Visit 12) + 4 day. For patients who are not entering into the open-label extension study, patients will gradually be tapered off of study medication. For patients who are entering the open-label extension study, patients will enter the transition phase where all patients will be on a dose of 0.2 mg/kg/day at the end of this phase. The end date of this period is considered to be the date recorded at Visit 13.

6.6. Pooling of Centers

There are approximately 60 sites participating in Studies 1501 and 1502 from US, Canada, Belgium, Denmark, France, Germany, Italy, Japan, Norway, Spain, Sweden, United Kingdom, and Australia. For Study 1502 Japan was added in 2019 whereas Europe and Australia started in 2016. Approximately 36 sites will contribute randomized subjects to Study 2. It is likely that the number of patients recruited by some sites will be small. The primary analysis will use data pooled across sites. Differences among regions may be explored if warranted.

6.7. Subgroups

Select efficacy and safety outputs may be further broken down by the following subgroups:

- Age strata: <6 years, ≥6 years.
- Japanese subjects, Non-Japanese subjects
- Sex
- Race

  SCN1A Mutation Yes/No

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

Subject disposition will be presented per treatment group and overall.

For describing the subject disposition, the following will be summarized by number and percentage:

- Subjects enrolled (only overall)
- Subjects enrolled but not randomized and reason for not-randomized (only overall)
- Subjects randomized
- SAF
- mITT
- PP
- Subjects assigned to SAF, mITT, PP and discontinued the study and reason.
- Number of subjects in the trial per trial period/phase (Titration Phase, Maintenance Phase, Follow-up Period) will be presented for SAF and mITT sets.
- Trial completers.
    - Trial completers continuing in the open-label extension study
    - Trial completers not continuing in the open-label extension study

For subjects enrolled but not randomized to treatment and for the reasons for not being randomized the denominator used to calculate the percentage will be the number of enrolled subjects. For all other calculations the denominator will be the number of subjects randomized.

All subject data will be listed using the enrolled population and sorted by treatment and site.

7.2. Demographic and Other Baseline Characteristics

Subject demographics and baseline characteristics will be summarized descriptively per treatment group and overall, for the SAF and mITT populations as well as for Japan and Non-Japan sub-groups.

The following demographic characteristics will be summarized:

- Age[Years]
- Categorical age as <6 years and ≥6 years.
- Sex
- Race
- Ethnicity
- Height [m]
- Weight [kg]
- BMI [kg/m2]

All subject demographics data will be listed for the enrolled population.

Below are conversions that may be applied:

Age at Study day 1 = (Study day 1) visit date - date of birth + 1) / 365.25 and truncated to complete years.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight(kg)/[Height$(m)^2$]

7.3. Medical History and Concomitant Diseases

Medical history will be summarized and sorted alphabetically, by primary System Organ Class and Preferred Term coded via the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects will be displayed for each System Organ Class and Preferred Term within treatment group.

Medical history will be presented for the SAF population.

All prior and concomitant medical history data of subjects will be listed for the enrolled population.

7.4. Other Baseline Characteristics

Other baseline characteristics such as epilepsy/seizure history and epilepsy genotype panel data will be descriptively summarized as per data type (categorical). Genetic data will be summarized as the proportion who have or do not have mutations of the SCN1A gene. Additional analyses of genetic data may be prepared in a separate report.

All subject baseline characteristics will be listed for the enrolled population.

7.5. Medication

7.5.1. Prior Medication and Concomitant Medication

Medication (collected on prior medications, and concomitant medications eCRF page) will be coded using the World Health Organization Drug Dictionary (WHO-DD) Format B3 Version Sep2017 or later.

The following algorithm will be used to define prior and concomitant.

Prior medications will be those with a stop date prior to first dose administration.

Concomitant medications will be defined as those medications that were initiated after study drug administration or those medications that were ongoing at the date of first study drug administration.

The medication will be assumed to be prior medication if it cannot be definitively shown that the medication did not start or continue during the treatment period.

If the start date or stop date of a medication is partially missing, the date will be compared as far as possible with the date of the start of administration of study drug. The following approach will be taken:

- If the start date of medication is complete and occurs on or after the day of the first full dose, the medication will be assumed concomitant. If the start date occurs prior to the first full dose date but the end date is on or after the first dose date or the medication is recorded as ongoing, the medication will be considered concomitant.
- If the start day is missing but the start month and year are complete, a medication will only be excluded as being concomitant if the start month/year is before the month/year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration.
- If the start day and month are missing but the start year is complete, a medication will only be excluded as concomitant if the start year is before the year of study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before study drug administration.

- If the start date is completely missing and the stop date is prior to first dose or completely missing, the medication will be assumed to be a prior medication.

Medication will be summarized and sorted alphabetically separately for prior and concomitant medication by Anatomical Therapeutic Chemical (ATC) categories (Level 2: pharmacological or therapeutic subgroup and Level 3: chemical or therapeutic or pharmacological subgroup) and WHO-DD drug code. For each medication the number and percentage of subjects will be displayed.

Medication summary tables will be presented for the SAF population.

All prior and concomitant medications/treatments will be listed for the enrolled population.

7.5.2. Prior and Concomitant Antiepileptic Treatments

Antiepileptic treatments (collected on the prior antiepileptic medications, and concomitant medications eCRF page) will be coded using the World Health Organization Drug Dictionary (WHO-DD) Format B3 Version Sep2017 or later. Anti-epileptic medications will be identified using any drug entered on the prior-antiepileptic medication.

Prior and concomitant antiepileptic medications will be defined and analyzed for the safety population similar to concomitant medications as described in Section 7.5.1.

All prior and concomitant antiepileptic treatments will be listed for the enrolled population.

8. Efficacy

The analysis of the primary and secondary efficacy parameters will be performed on the mITT population, except where noted.

The primary and key secondary efficacy analyses will be repeated on the PP Population.

All primary and key secondary variables will be analyzed for data obtained for the T+M period, and will be repeated for data obtained during the M period only.

8.1. Primary Efficacy Endpoint and 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. For each subject, the CSF will be calculated from all available data collected during the Baseline and T+M Periods, and the treatment group mean convulsive seizure frequency per 28 days (MCSF) will be calculated for the baseline and T+M period.

The baseline period is the 42 days immediately preceding the Randomization visit and the T+M period is planned for 14 weeks. However, actual durations will be computed for each subject based on the individual subject's start and stop dates for each period, except that if the baseline period is longer than 42 days, the average for the baseline period will be taken over the 42 days immediately preceding the Randomization visit.

The convulsive seizure frequency will be counted from the daily diary records provided by the Subject or Parent/Caregiver.

For any individual subject, the convulsive seizure frequency per 28 days during the baseline period (CSF_B) will be derived as follows:

$$CSF_B = \frac{28 \times \text{Total number of convulsive seizures during the Baseline Period}}{\text{Total number of days in the Baseline Period with nonmissing diary data}}$$

For each treatment group, the mean is obtained by averaging over the subjects in the treatment group.

Similarly, for each subject, the convulsive seizure frequency per 28 days for the T+M period ($MCSF_{T+M}$) is derived as below:

$$CSF_{T+M} = \frac{28 \times \text{Total number of convulsive seizures in the T + M period}}{\text{Total number of days in the T + M period with nonmissing diary data}}$$

The percentage change from baseline for any individual subject will be estimated by

$(CSF_{T+M} - CSF_B)*100/CSF_B$

The difference from baseline will be estimated by $CSF_{T+M} - CSF_B$.

Corresponding treatment group means are designated with "M" preceding the quantity. For each treatment group, descriptive statistics for MCSF during baseline, T+M and M only, as well as the differences and % changes from baseline, will include the number of observations, mean, standard deviation, median, minimum and maximum, overall and by age group (<6 years, ≥6 years).

Primary Analysis

T+M Period:

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.

The primary endpoint (CSF_{T+M}) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group (three levels) and age group (< 6 years, ≥6 years) as factors, log baseline CSF_B as a covariate and log CSF_{T+M} as response. Treatment group mean differences from placebo will be estimated via least squares means from the analysis model along with 95% confidence intervals and associated 2-sided p-values. Estimated treatment differences and CI endpoints will be exponentiated for presentation.

The null hypothesis

$$H_0: \mu_{Z0.8} - \mu_P = 0,$$

will be tested against the alternative

$$H_A: \mu_{Z0.8} - \mu_P \neq 0,$$

where $\mu_{Z0.8}$ and μ_P represent the ZX008 0.8 mg/kg and Placebo group means (on the log scale), respectively.

Rejection of the null hypothesis in favor of the alternative, in the presence of a statistically significantly smaller mean convulsive seizure frequency for the treatment group compared to the placebo group, (two-sided p-value < 0.05) will be regarded as evidence of a treatment benefit in favor of the 0.8 mg/kg group.

Sample SAS code for the ANCOVA described above is as follows:

```
proc glm data=temp;
        class agegrp trtp;
        model csftm = bcsf agegrp trtp / SS3;
        lsmeans  trtp / pdiff stderr;
```

where trtp = randomized treatment group (with codes 1, 2, 3 indicating placebo, 0.2 mg, and 0.8 mg groups).

bcsf = log(CSF_B),
csftm = log(CSF_{T+M} + 1)
agegrp = age group.

Additional statements may be used to obtain estimates and associated 95% confidence intervals. Endpoints of the CIs may be exponentiated to obtain CI on the original scale. Fitted values and residuals will be plotted to check model assumptions.

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 ANCOVA will be used to analyze the data, with ranks of the baseline CSF_B as a covariate and ranks of CSF_{T+M} as response, and the results will be used to assess the primary objective. If normality assumptions are not met, the results of the nonparametric test will be used to assess the primary objective.

The primary analysis described above will be repeated using data from the Maintenance period only as response. For subjects who did not reach the Maintenance period, their Transition period data will be used to represent their M period data.

A similar ANCOVA model will be used, and if distributional assumptions are not met, a nonparametric analysis will be performed.

Treatment by baseline seizure category interaction: The primary analysis described above will be repeated with baseline seizure frequency as a categorical variable, rather than a covariate. Baseline seizure frequency per 28 days will be categorized as either < 10; 10-50; or >50.

Supplementary and Sensitivity Analyses

Per protocol Analysis

Additionally, the primary efficacy analysis will be repeated on the per protocol population (which excludes subjects with important protocol deviations that may affect the inference on efficacy such as a change in dose or type of concomitant AED medication).

Percentage Reduction from Baseline

The ANCOVA employed in the primary analysis uses log CSF_{T+M} as the response adjusts for baseline seizure frequency by incorporating CSF_B as a factor in the model. The alternative approach described here calculates the percentage change in CSF from baseline directly and uses that quantity as the response variable in an ANCOVA model. Specifically, the ANCOVA will use the percentage change from the T+M period to baseline as the response variable, baseline CSF as a covariate, and treatment and age stratum as classification factors. The analyses will be repeated for the M period only using the baseline as covariate.

If the distributional assumptions for the parametric analysis are not met, a nonparametric ANCOVA will be used for the ranks of the dependent variable as response, using the ranks of the baseline as covariate.

Criteria for Establishing Efficacy

While several supportive and/or supplementary analyses are specified above, the main criterion for demonstrating efficacy will be the primary analysis using the log transform for the mITT population. It is conceivable that some or all of these supplemental analyses may not reach statistical significance. However, it is expected that the direction of effect will be in favor of the test treatment. As an example, a statistically significantly smaller least squares adjusted MCSF for the treatment group compared to placebo, in the presence of a smaller proportion of subjects on 0.8 mg/kg than Placebo subjects increasing their dose of concomitant AEDs will be strong evidence for efficacy of the experimental treatment.

8.2. Secondary Efficacy Endpoint(s) and Analyses

8.2.1. Key Secondary Analysis

MCSF for ZX008 0.2 mg/kg/day versus Placebo

The MCSF during the T+M period will be analyzed and compared between the ZX008 0.2 mg/kg/day group and the placebo group using the same methods employed for the primary analysis. Following the same strategy as the ZX008 0.8 mg/kg/day comparison, a nonparametric analysis using ranks will be used for the ZX008 0.2 mg/kg/day comparison if the assumptions of the parametric ANCOVA model are not met.

The analysis will be repeated for the M period.

Proportion with ≥50% Reduction from Baseline in Convulsive Seizure Frequency

Subjects with a percent reduction in convulsive seizures of at least 50 percentage points from baseline will be identified and the overall proportion within each treatment tabulated. That is, the proportion of subjects in the ZX008 0.8 mg/kg/day group who have a decrease in convulsive frequency of at least -50 percentage points will be compared to the analogous proportion in the placebo group.

Similarly, the proportion of subjects in the ZX008 0.2 mg/kg/day group who have a change in convulsive frequency of at least -50 percentage points will be compared to the analogous proportion in the placebo group.

The comparison between treatment groups will be made using a logistic regression model that incorporates the same factors as the ANCOVA used in the primary analysis. This will model a categorical response variable (achieved 50 percentage point reduction, yes or no) as a function of treatment group (ZX008 and placebo) and age group (< 6 years, ≥6 years). Comparisons between treatment groups will also be made using pairwise Fisher's exact tests since the logistic regression models may not converge in all circumstances.

Raw descriptive statistics will be presented by treatment group, and will include the number and proportion of subjects < 6 years, ≥6 years, and overall achieving the reduction along with the model estimated odds ratio (including a 95% confidence interval) and p-values from both logistic regression and Fisher's test for comparison of ZX008 0.8mg/kg/day to placebo and ZX008 0.2mg/kg/day to placebo separately.

Longest Interval between Convulsive Seizures

The longest interval between convulsive seizures will be analyzed.

For each subject, the longest interval between convulsive seizures will be calculated over the entire T+M period. This will be derived as the maximum of the number of days between consecutive convulsive seizures. The intervals between consecutive convulsive seizures will be calculated as below, after which the longest interval between convulsive seizures will be derived.

If a subject has two consecutive days of missing diary data, the current seizure-free interval will be ended on the first date of missing diary data, and a new one begun on the next date that diary data are available and no seizure occurs. [In that case, for purpose of calculation of this variable, all intervening days, after the 2nd day, with missing diary data, will be assumed to have a convulsive seizure occurrence, until the first available date with non missing diary data.]

Let Date0 (=Day1) be the first day of treatment. If convulsive seizure occurs on five days having dates as Date1, Date2, Date3, Date4 and Date5, where Date5>Date4>Date3>Date2>Date1≥Date0, and let LDT = Last date of treatment in the maintenance period, where LDT ≥ Date5, then the time interval between convulsive seizures will be calculated as follows:

I1=Date2 - Date1

I2=Date3 - Date2

I3=Date4 – Date3,

I4=Date5 – Date4.

For completeness, we calculate the time to the first seizure as

I0=Date1 – Date0,

and the time from the last seizure to end of treatment as

I5 = LDT – Date5.

Here the duration of the longest interval =Maximum (I0, I1, I2, I3, I4, I5).

If the subject does not experience a seizure during treatment, then the last available diary date will be used to compute the duration of the longest interval as follows:

The longest interval=last available diary date – Date0

The median time of the longest convulsive seizure-free interval will be presented. Additional summary statistics will be presented, including mean, minimum, maximum, the 25th and 75th percentiles, 95% confidence intervals on the difference in medians between groups (Hodges-Lehman estimator).

The Wilcoxon rank sum test will be used to test for differences between each treatment arm and placebo, and the p-value from this test will be presented. A histogram presenting the percentage of subjects whose longest seizure free interval is <10, 11-20, 21-40, 41-60, 61-84, and ≥84 days will accompany all descriptive statistics and all data will be provided in a data listing.

8.2.2. Additional Secondary Endpoint Analysis

Number of Convulsive Seizure Free Days

Convulsive seizure free days will be taken from the parent/caregiver diary data.

A convulsive seizure free day will be defined as a day for which diary data are available and no convulsive seizures have been reported. The total number of convulsive seizure free days will be summed for the entire T+M period and similarly for the baseline period.

Seizure free days per 28 days at baseline = (number of seizure free days during baseline)*28/(number of days during baseline with non-missing diary data)

Seizure free days per 28 days during T+M Period = (number of seizure free days during T+M Period)*28/(number of days during T+M Period with non-missing diary data)

Statistical comparison of treatment groups and placebo on the number of seizure free days per 28 days during T + M using the baseline as covariate will be done with a similar approach as the primary analysis.

Responder Analyses: Proportion with ≥25 , 75% or 100% Reduction from Baseline in Convulsive Seizure Frequency

A response curve will be generated for the mITT population. This graph will plot the % of subjects (y-axis) against percentage reduction in seizure frequency per 28 days in the T+M and M periods (x-axis). The horizontal axis will be the % reduction, and the vertical axis will be the % of subjects achieving ≥ that % reduction. In the graph, subjects experiencing an increase or no decrease in seizure frequency (i.e., ≤0 % reduction) will be regarded as having a 0% reduction in seizure frequency. Hence the ordinate for the 0 time point may not necessarily be at 100%. For example, if 15% of subjects have no reduction in seizure frequency during T+M period compared to the baseline period, the graph will start on the y-axis at 85%. The graph will be generated for all subjects, by treatment group.

- The proportion achieving a ≥25% reduction from baseline in convulsive seizures will be analyzed for both treatment groups (ZX008 0.2 mg/kg/day and ZX008 0.8 mg/kg/day) comparing independently with placebo, using the same methods employed for the ≥50% reduction from baseline endpoint.
- The proportion achieving a ≥75% reduction from baseline in convulsive seizures will be analyzed for both treatment groups (ZX008 0.2 mg/kg/day and ZX008 0.8 mg/kg/day) comparing independently with placebo, using the same methods employed for the ≥50% reduction from baseline endpoint.
- The proportion achieving a 100% reduction from baseline in convulsive seizures, i.e., seizure-freedom, will be analyzed for both treatment groups (ZX008 0.2 mg/kg/day and ZX008 0.8 mg/kg/day) comparing independently with placebo, using the same methods employed for the ≥50% reduction from baseline endpoint.
- The proportion of subjects with near seizure freedom during the T+M period. Near seizure-freedom will be defined as having 0 or 1 seizures leading to a drop in the T+M period. These are additional secondary endpoints. Groups will be compared using the same methods employed for the ≥50% reduction from baseline endpoint.

A second response curve will be generated in which subjects who experience an increase in seizure frequency will be represented on the curve at horizontal axis at the position representing their increase in seizure frequency. Increases in seizure frequency will be represented to the left of the vertical axis on the figure.

Change from Baseline in Non-Convulsive Seizure Frequency

Algorithms for calculating mean non-convulsive seizure frequency and percent change from baseline will follow the methods as described for the primary endpoint using a nonparametric ANCOVA to analyze the data, with ranks of the baseline non-CSF_B as a covariate and ranks of non-CSF_{T+M} as response,.

Change from baseline in non-convulsive seizures will be presented by seizure types (e.g., focal, generalized).

Change from Baseline in Convulsive + Non-Convulsive Seizure Frequency

The change from baseline in convulsive + non-convulsive seizure frequency will be calculated as described for the primary endpoint, but considering both convulsive and non-convulsive seizures.

Algorithms for calculating mean convulsive and non-convulsive seizure frequency and percent change from baseline will follow the methods as described for the primary endpoint using a nonparametric ANCOVA to analyze the data, with ranks of the baseline convulsive + non-CSF_B as a covariate and ranks of convulsive + non- CSF_{T+M} as response,

Incidence of Rescue Medication Usage

Use of rescue medication is recorded on the daily diary. In the event of prolonged seizures or status epilepticus, rescue medication is administered according to each subject's personalized regimen consisting of one or more medications. If the first rescue administration does not control the seizures, a second or even third round might be administered. They second and third round might use different medications or different doses than the first round of rescue meds.

Rescue medication will be summarized by treatment group and by active treatment vs. Placebo for the following:

- The number of days rescue medication was taken (normalized to 28 days) will be summarized separately for the Baseline ,T+M periods and change from baseline by the mean (SD) as well as the median and range. Multiple medications taken on the same day will be counted once for that

day. The ZX008 group will be compared to the placebo group using a rank ANCOVA analogous to that described in Section 8.1 Primary analysis. Specifically, the rank ANCOVA will use the ranks of rescue medication frequency during T+M as the response, and will incorporate treatment group as a factor and the ranks of rescue medication frequency during Baseline as a covariate.

- The number of medications used per episode will be summarized using similar descriptive statistics as above. Rescue medications related to an episode of SE are considered to be all rescue administered on the day of the SE (or seizure lasting >10 min). If more than one episode of SE or a seizure lasting >10 min occurred in a single day, the rescue medication for that episode is all rescue administered after the seizure until the start time of the next prolonged seizure.

Incidence of Hospitalization to Treat Seizures

Hospitalization data will be captured in the CRF and will be used to calculate incidence.

The number and percentage of subjects who utilized medical center care to treat a seizure will be presented by treatment group for the T+M period. Statistical comparisons of the differences between treatment and placebo groups will be based on Cochran-Mantel-Haenszel test stratified by age group.

Incidence of Status Epilepticus

The incidence of status epilepticus will be evaluated based on cases captured as such with treatment at hospitals or other treatment centers, those entered as adverse events (including SAEs) into the safety database, and also as convulsive seizures lasting longer than 10 min from the seizure diary. A single seizure meeting more than one of these criteria will be counted once. According to the ILAE, seizures of this duration are to be considered SE.

The number and percentage of subjects with status epilepticus recorded as an AE will be presented by treatment group for the baseline and the T+M period per 28 days.

In addition, the number and percentage of subjects who experience at least one convulsive seizure with duration >10 min will be reported for the baseline and T+M period.

All seizures recorded in the AE database as status epilepticus should also be included in the seizure diary. An edit check will be performed to identify the overlap between seizures identified as AE of SE and seizures entered into the diary as seizures > 10 min. The “calculated” number and percentage of subjects experiencing SE will be presented by treatment group, defined as individuals who experience either an AE of SE, medical treatment for SE, or a seizure lasting longer than 10 min. Each subject will be represented once regardless of incidence.

A statistical comparison of the differences between the ZX008 0.8 mg/kg/day and placebo groups will be based on a logistic regression model with a categorical response (experienced at least one SE as an AE or a seizure >10 minutes during T+M, yes or no) as a function of treatment group (active or placebo), age group (< 6 years, ≥ 6 years), and a categorical baseline variable (experienced at least one SE as an AE or a seizure >10 minutes during Baseline, yes or no). An anolgous model will be used to compare the ZX008 0.2 mg/kg/day group to placebo.

The number of incidences of status epilepticus will be cross-tabulated against the incidences of rescue medication uses (Yes/No). Cochran–Mantel–Haenszel test (CMH) test will be used to test the general association between incidences of SE and rescue medication uses.

Duration of Prolonged Seizures

Duration of convulsive seizures at baseline and on treatment will be presented by treatment group using categories as <2 min, 2-10 min and >10 min.

To obtain a baseline probability distribution for the 3 categories, we will proceed as follows: For each subject, we will calculate the percentage of their total number of baseline seizures that is in each category. (For example, if the subject had 5 seizures, with 2 in the first category and 3 in the last category, their percentage distribution would be 40%, 0%, and 60% in the <2, 2-10, and >10 categories. We can calculate similar numbers for the next subject, and so on.) We will then average these over all subjects to obtain the % of subjects' seizures that were <2 min in duration, the % between 2-10 min in duration, and the % >10 min in duration. These 3 percentages should total 100%. Thus we will obtain a distribution of seizure duration for baseline.

Using the seizure duration data obtained for the T+M period, we will proceed similarly, to obtain a distribution for the T+M period.

It is expected that treatment with ZX008 will result in shorter duration of seizures (as well as fewer seizures) during T+M compared to placebo, i.e., the probability of longer seizures (>10 min) will be higher for the placebo group than for the ZX008 arms. This may be assessed by comparing the probability of a >10 min seizure during T+M to the same during baseline, for a treatment group, to the same for the Placebo group. It is expected that the ZX008 group will have greater odds of a reduction in proportion of seizures >10 min than the Placebo group. However, treatment with ZX008 may result in fewer seizures overall yet the duration of residual seizures may not be shorter. Should the primary or key secondary endpoints be positive for a given dose(s), but the duration of seizures not be shortened per above, exploratory evaluations may be undertaken to better understand the effect.

Clinical Global Impression – Improvement Rating, as assessed by the Parent/Caregiver

The parent/caregiver and the investigator will rate their global impression of the subject's condition at each clinic visit after randomization: end of Titration period (Visit 6), Maintenance period (Visit 8 and 10), and at End of study (Visit 12).

The CGI-I scale measures the change in the subject's clinical status from a specific point in time, i.e., the Baseline Period. The CGI-I 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 mean (SD) CGI-I score, and the number and percentage of subjects who showed improvement (i.e., had a score of 3 or lower), and the number and percentage who did not improve (i.e., had a score of 4 or higher) will be presented for each for each treatment group at each assessment timepoint. Each assessment time point will also include a comparison between each active treatment and the placebo group using the Cochran-Mantel-Haenszel test stratified by age group, and a frequency distribution of the

number and percentage of subjects in each category in the scale. A histogram of the frequency distribution will be presented.

The number and percentage of subjects who were much or very much improvement (i.e., had a score of 2 or lower), and the number and percentage who were minimally improved or did not improve (i.e., had a score of 3 or higher) will also be presented for each for each treatment group at each assessment timepoint as an exploratory analysis.

Individual subject CGI data will be listed.

Clinical Global Impression – Improvement Rating, as assessed by the Principal Investigator

CGI-I score data assessed by the principal investigator will be summarized and analyzed using the same methods used for CGI-I score data recorded by parent/caregiver as above.

Quality of Life in Childhood Epilepsy (QOLCE) Scale

The parent/caregiver will complete this questionnaire for the QOLCE. This assessment 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, at baseline period (Visit 3), at Maintenance period (Visit 8) and at End of study/ET (Visit 12). There is also one question on overall quality of life, administered as part of the QOLCE.

The QOLCE scores items with a possible 5 point response. [Not including "6", "Not Applicable."] To calculate subscale scores, the 5 point item scores will first be reverse coded as necessary so that scores of 5 represent the best possible response and 1 represents the worst possible response. Item scores will then be transformed to a 0-100 scale as follows: 1-0, 2-25, 3-50, 4-75, 5-100. After transformation, a score for each subject for each subscale is calculated by averaging that subject's responses to each item in the subscale. [A value of 0 represents the lowest or poorest score and 100 reflects the highest level of functioning.] The 16 subscale scores per subject are then averaged to obtain an overall quality of life score for each subject. The mean and SD across all subjects are then calculated for each subscale, including the overall quality of life score. The higher the subscale and overall quality of life scores, the better the response.

Table 2: Subscale of QOLCE:

Domain	Subscale	Item
Section 3: Physical	Physical Restrictions	3.1 a-j
Section 3: Physical	Energy/Fatigue	3.2 a,b
Section 4: Well-being	Depression	4.1 a,d,e,l
Section 4: Well-being	Anxiety	4.1 b,g,j,n,o,p
Section 4: Well-being	Control/helplessness	4.1 c,f,h,i
Section 4: Well-being	Self-esteem	4.1 k,m,q,r,s
Section 5: Cognition	Attention/Concentration	5.1 a,d,e,f,g
Section 5: Cognition	Memory	5.1 j,k,l,m,n,o
Section 5: Cognition	Language	5.1 p,q,r,s,t,u,v,w
Section 5: Cognition	Other Cognitive	5.1 b,c,h
Section 6: Social Activities	Social Interactions	6.1 c,f,h
Section 6: Social Activities	Social Activities	6.1 a, e, 6.2

Section 6: Social Activities	Stigma Item	6.1 i
Section 7: Behavior	Behavior	7.1 a, c,f,g,h,i,j,k,l,m,o,q,r,s,t
Section 8: General Health	General Health Item	8.1
Section 2 (USA Version) or Section 9 (Australia Version)	Quality of Life Item	2.1 or 9.1
Overall Quality of Life *		Average of 16 subscale scores*

*An Overall Quality of Life Score can be computed by adding each subscale score for each individual and then dividing by 16.

For each treatment group at Baseline and End of Study/ET, the mean (SD) score will be presented for each QOLCE subscale and for the overall quality of life score.

In addition, the change from baseline in the overall QOLCE will be calculated for each subject by subtracting the baseline overall score from the overall score measured at End of Study/ET. The change from baseline for each treatment group will be summarized by the mean (SD) and treatment groups will be compared using pairwise Wilcoxon tests.

Individual subject data for the domains will be listed.

Quality of Life of the Parent/Caregiver using EQ-5D-5L Scale

The impact on the quality of life of the parent/caregiver responsible for a patient with DS will be assessed at Baseline (Visit 3) and at End of study (Visit 12) using the EQ-5D-5L. The responsible parent/caregiver was permitted to opt out of completing the EQ-5D-5L.

The EQ-5D-5L health questionnaire is a health-related quality of life instrument with 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 possible levels: no problems, slight problems, moderate problems, severe problems and extreme problems.

The summary of results will follow the EQ-5D-5L guideline results presentation. For the “Health Profiles” descriptive system summary results will show the number, and proportion (%) of subjects in each Item score (No Problems, Slight Problems, Moderate Problem, Severe Problem, Extreme Problems) by treatment at baseline and at the end of study. In addition, the item scores will be classified into two categories as “No Problems” and “Problems,” the latter comprised of slight, moderate, severe and extreme problems. Summary results will show number of patients and proportion (%) with “No Problems” and with “Problems” by treatment at baseline and at end of study.

For the VAS measure of overall self-rated health status, descriptive statistics summary results will be presented for the VAS score showing number of subjects, mean, standard deviation, median, and range by each treatment at baseline and end of study time points.

The change from baseline in VAS will be calculated by subtracting the VAS score at baseline from the VAS score obtained at End of Study/ET. The change in VAS will be summarized using descriptive statistics, and treatment groups will be compared using pairwise Wilcoxon tests.

The quality of life of parent/caregiver individual data will be listed using EQ-5D-5L scale.

Parent/Caregiver Assessment using HADS Scale

The HADS is a tool commonly used to determine the levels of anxiety and depression that a person is experiencing and is administered to the primary parent/caregiver to assess these symptoms longitudinally during the study. The responsible parent/caregiver was permitted to opt out of the HADS. The HADS is a 14-item scale that generates ordinal data for two dimensions: 1) Anxiety and 2) Depression. Seven of the items relate to anxiety and 7 relate to depression.
Each item has 4 possible answers rated 0-3. All answers to the items for a dimension with their respective rating are added resulting in a range for each dimension from 0-21. Scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress.

Summary descriptive statistics including the mean and SD will be generated separately for the Anxiety and Depression dimensions at both Baseline and at End or Study/ET. In addition, each subject will be categorized at each time point based on the score cut-offs below which were validated on adult patients in a treatment setting.

Score	Category
0-7	Normal
8-10	Borderline abnormal
11-21	Abnormal

Summary statistics will include number and proportion (%) of subjects in each of the categories above at each study visit.

In additional, the total score for Anxiety and Depression will be generated. Descriptive statistics summaries including mean, median, standard deviation, median and range will be summarized for each treatment at Baseline and End of Study/ET.

The change from baseline for each subject will be calculated by subtracting the total Anxiety and Depression score measured at Baseline from the analogous score measured at End of Study/ET. The change from baseline will be summarized by descriptive statistics and the difference between treatment groups will be assessed using pairwise Wilcoxon tests.

The individual item outcomes will be presented in the subject data listing.

Pediatric Quality of Life Inventory (PedsQL 4.0 Generic Core) Scale

The PedsQL 4.0 is a quality of life scale that measures four functional areas (physical, emotional, social, and school functioning). The scale is available in age-appropriate instruments with child self-report and parent proxy-report formats. In this study, the age appropriate categories for the administration of the instrument were ages 2-4, 5-7, 8-12 and 13-18 years, and the Parent Reports were used.

There are 8 items for Physical Functioning, and 5 questions each for Emotional, Social, and School Functioning. Each of the responses to the 23 items is initially scored on a 5 point Likert scale from 0 (Never) to 4 (Almost always). Scores will be linearly transformed to a scale of 0 to 100, where 0=100, 1=75, 2=50, 3=25 and 4=0, and higher scores mean better health related quality of life. If more than 50% of the items in the scale are missing, the scale scores should not be computed. A mean score is calculated as the sum of the items over the number of items answered. If some of the answers on a scale are missing but 50% or more of the items in the scale are completed, then impute the mean of the

completed items in a scale. The scaled results will be combined across age categories to produce a single score for each functional area.

A Psychosocial Health Summary score is computed as the sum of the items over the number of items answered in the Emotional, Social, and School Functioning Scales.

A Physical Health Summary score is made up of the Physical Functioning Scale Score.

The Total Score is computed as the sum of all the items over the number of items answered on all the Scales.

Descriptive statistics at both Baseline and EOS/ET will be provided for the Psychosocial Health Summary score, the Physical Health Summary score and Total Score.

The change from baseline for the Total Score will be calculated for each subject by subtracting the Total Score measured at Baseline from the Total Score measured at End of Study/ET. The change from baseline will be summarized with descriptive statistics and treatment groups will be compared on the Total Score using pairwise Wilcoxon tests.

Pediatric Quality of Life Inventory (PedsQL 2.0 Family Impact Module) Scale

The PedsQL™ Family Impact Module was designed to measure the impact of pediatric chronic health conditions on parents and the family. The PedsQL™ Family Impact Module measures parent self-reported physical, emotional, social, and cognitive functioning, communication, and worry. The Module also measures parent-reported family daily activities and family relationships.

There are 6 items for Physical Functioning, 5 items each for Emotional Functioning, Cognitive Functioning and Worry, 4 for Social Functioning, and 3 for Communication. There are additionally 3 questions for Daily Activities and 5 for Family Relationships.

Each of the responses to the 36 items is initially scored on a 5 point Likert scale from 0 (Never) to 4 (Almost always). Scores will be linearly transformed to a scale of 0 to 100, where 0=100, 1=75, 2=50, 3=25 and 4=0, and higher scores mean better health related quality of life. If more than 50% of the items in the scale are missing, the scale scores should not be computed. A mean score is calculated as the sum of the items over the number of items answered. If some of the answers on a scale are missing but 50% or more of the items in the scale are completed, then impute the mean of the completed items in a scale.

The Parent HRQL Summary Score (20 items) is computed as the sum of the items divided by the number of items answered in the Physical, Emotional, Social, and Cognitive Functioning scales.

The Family Functioning Summary Score (8 items) is computed as the sum of the items divided by the number of items answered in the Daily Activities and Family Relationships scales.

The Total Score is the sum of all 36 items divided by the number of items answered.

Descriptive statistics for baseline and EOS/ET will be provided for the summary scores.

8.2.3. Exploratory Analyses

Exploratory analysis may be performed by comparing of ZX008 0.2 and 0.8 mg/kg/day doses on primary, secondary, safety and PK endpoints.

Thus, all comparisons planned for ZX008 to placebo may be repeated to compare the ZX008 0.2 and 0.8 mg/kg/day doses.

Additional exploratory analyses may include descriptive summaries of the primary endpoint by:

- SCN1a Mutation Status
- seizure type
- baseline seizure frequency
- Age (greater than or equal to 13 years at baseline)
- Concomitant AED: VPA, CLB, VPA+CLB
- Number of concomitant AEDs

9. Analysis Of Pharmacokinetics

The bioanalytical methods for the determination of individual plasma concentrations of fenfluramine and its metabolite (norfenfluramine) will be reported together with the plasma concentration results in separate bioanalytical reports. These bioanalytical reports will be issued as a separate report.

10. Safety

All safety analyses will be performed for the Safety population (SAF) and will be reported by treatment group as well as ZX008 combined for the 16-week treatment period unless noted otherwise.

10.1. Extent of Exposure

Treatment exposure data will be summarized and analyzed for the SAF population.

Duration of total exposure to ZX008 (i.e., time on treatment (in days)) will be calculated per subject as the number of days with IMP intake during the trial, and will be summarized using n, mean, standard error, median, minimum, Q1, Q3 and maximum.

This will be calculated as:

Date of last IMP intake – Date of first IMP intake + 1

Time on treatment will be summarized by treatment group.

10.2. Treatment Compliance

Study medication is to be administered twice daily, and compliance is recorded in the eDiary as full (both doses), partial (less than full daily dose) or missed (both doses) each day. From this, compliance will be calculated by assuming that a missed dose=0% of dose consumed, partial=50% of dose consumed, and full=100% of dose consumed. For each subject, a daily compliance score will be thus obtained.

Compliance will be summarized for the SAF and mITT populations over the course of T+M and Maintenance only, reported by treatment group.

10.3. Adverse Events

An AE is defined as 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 the titration/transition period (Visit 13). For patients who continue into the open-label extension study, AEs of special interest will continue to be monitored for up to 6 months after the last dose of study medication.

A TEAE is defined as any AE that based on start date information occurs after the first intake of study treatment. Safety tables will present TEAE data by assigned treatment group through Visit 13. All other AEs occurring after enrollment and prior to the first administration of study treatment are defined as non-treatment emergent AEs (non-TEAEs).

AEs are categorized as related or unrelated. If the AE is thought to be definitely, probably or possibly related to study drug then it is to be categorized as related. Possibly or definitely unrelated is categorized as unrelated. Any missing relationship will be considered as "related."

The severity of AEs (whether nonserious or serious AEs) will be assessed by the investigator as follows:

Severity Definition of Adverse Events:

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

Any missing severity will be imputed as “severe.”

The original terms used by the investigators in the eCRFs to identify AEs will be coded using the most recent version of the MedDRA implemented by the sponsor at the end of the study.

Overview of Adverse Events:

The number and percent of patients with at least one of the following events will be summarized in an overall summary table:

- TEAE.
- Serious TEAE
- Related TEAE
- Related serious TEAE.
- Severe TEAEs
- Adverse events of special interest
- TEAEs that lead to death
- TEAE leading to discontinuation of study treatment

The percentage denominator for the calculation of percentage will be the number of subjects in the SAF.

Incidence of Treatment Emergent Adverse Events

The following summaries will display the number and percentage of subjects with an adverse event as well as the corresponding number of events by system organ class (SOC) and preferred term (sorted alphabetically):

- All TEAEs
- Serious TEAEs
- TEAEs by Maximum Severity
- Study Drug Related TEAEs
- All AEs that lead to premature discontinuation from the study

Additional summary tables will tally the number and percent of subjects in each treatment group who experience an AE that occurs in at least 2%, and at least 5%, of subjects. The summary will be presented by preferred term in decreasing order of incidence.

A table will be provided for TEAEs (preferred term) where the percentage of subjects in a ZX008 arm who experience the event exceeds the percentage of subjects in the Placebo group with the event and occurs with a frequency of at least 2%.

No inferential statistical methods (i.e., methods that yield p-values) will be used to compare treatment groups on the frequency or severity of AEs.

These summaries will be provided for the T+M period.

Additionally, the following listings will be produced for all enrolled subjects:

- All AEs, events considered to be TEAE will be identified in the listing
- Serious AEs
- AEs that lead to premature discontinuation from the study
- Deaths

Adverse Events by Age and Gender

The following summary tabulations will be provided to explore the incidence of AEs within age and sex subgroups:

- All TEAEs by Age (<6 years, ≥6 years)
- All TEAEs by Sex (Females, Males)

Adverse Events by Concomitant Medication Usage

The following summary tabulations will be provided to explore the incidence of AEs by concomitant medication usage:

- Valproate
- Clobazam
- Topiramate

Adverse Events by Contry

The following summary tabulations will be provided to explore the incidence of AEs by contry:

- Japan
- Non-Japan

Adverse Events of Special Interest (AESI)

As per ICH guidance (E2F Development Safety Update Report [2011]), the sponsor has identified the following AESIs for the ZX008 in below Table 6.

Table 6 – Adverse Events of Special Interest:

CV/Respiratory
• Chest pain – any pain in sternal area that is described for example as crushing, burning, sharp, stabbing or dull.
• Dyspnea/shortness of breath – any signs of difficult or labored breathing unrelated to a

previous medical condition that has not worsened.
• Persistent cough – longer than 4 weeks without a confirmed identified pathogen (or any other persistent cough that the investigator feels is suspicious).
• 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.
• Jugular venous distention- visible bulging of the external jugular veins on either side of the neck
• New onset heart murmur
• Pulmonary rales – an abnormal respiratory sound heard during auscultation of the lungs, which is also described as a crackle.
• 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.
• 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
• Signs on ECHO indicative of potential valvulopathy 1. valve regurgitation (aortic or mitral) 2. ≥ mild valve regurgitation (tricuspid or pulmonary) 3. Mean Mitral valve gradient ≥ 4 mmHg 4. Mean Aortic valve gradient ≥ 15 mmHg 5. Mean Tricuspid valve gradient ≥ 4 mmHg 6. Mean Pulmonary valve gradient ≥ 21 mmHg
• 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
Metabolic/Endocrine
• Elevated prolactin level ≥2x above the upper limit of normal (ULN)
• Galactorrhea
• Gynecomastia
• Increase in fasting serum blood glucose ≥2x ULN
• Hypoglycemia – serum blood glucose more than 20% below the glucose level on Day -1 value or more than 10% below LLN (reference range 60 – 140 mg/dL)

Neuropsychiatric
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

MedDRA SMQs will be employed as applicable to identify each AESI category or manually assigned through review. This will be completed and documented prior to study unblinding.

Adverse events of special interests will be summarized by treatment group and by system organ class and preferred term for the T+M Period.

All adverse events of special interest will listed separately.

10.4. Laboratory Evaluations

Laboratory safety parameters will be analyzed by a central laboratory using standard validated methods.

All laboratory safety data will be collected as per the schedule of assessments.

The following continuous laboratory parameters will be analyzed:

1. Hematology: hemoglobin, hematocrit, erythrocytes, erythrocyte mean corpuscular volume, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets
2. Blood Biochemistry: albumin (ALB), alkaline phosphatase (AP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2), chloride (Cl), creatinine, creatine kinase, gamma-glutamyl transferase (GGT), globulin, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), thyroid function, thyroid stimulating hormone (TSH), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid.
3. 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
4. Coagulation: Prothrombin time (PT)/International normalized ratio (INR), activated partial thromboplastin time (PTT)
5. Whole blood cannabidiol
6. 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.
7. Urine pregnancy test: Urine pregnancy testing will be performed in female subjects of childbearing potential.
8. Urine THC panel

Observed continuous laboratory data will be descriptively summarized by type of laboratory test/parameter by treatment group. Changes from baseline will also be presented for all continuous laboratory parameters by treatment group over time.

Categorical laboratory parameters will be summarized by presenting the number and % of subjects by visit and by treatment arm.

All laboratory values (including invalid values, reference ranges, and possible flags (low, high,)) will be presented in the subject data listings.

A listing of subjects with Potentially Clinically Significant (Extreme) laboratory results will be provided.

A listing of subjects with markedly extreme abnormal laboratory results will be provided, and additional explorations of the data may be conducted as warranted. Additionally, summaries of abnormal lab results by parameter will be provided to investigate changes in platelet count and prolactin in greater detail. The summaries include:

- Subjects with decrease (≥25% from baseline) in Platelets count with normal platelet count at baseline
- Subjects with decrease (≥25% from baseline) in Platelets count relative to baseline (whether normal or abnormal) platelet count
- Subjects with increase (≥25% from baseline) in prolactin with normal baseline
- Subjects with increase (≥25% from baseline) in prolactin with normal baseline, and had seizure event within 48 hours prior to prolactin

10.5. Vital Signs

Vital signs data including blood pressure, heart rate, temperature, respiratory rate, weight, and BMI will be documented for subjects during study at screening visit (visit 1), randomization (visit 3) prior to first dose of study medication, titration period (visit 6), and maintenance period (visit 8 and visit 10) and at EOS visit (visit 12).

The mean value and change from baseline to each on-study evaluation will be summarized for vital signs and weight by treatment group. Vital signs, Weight and BMI data will be presented for each patient in a data listing.

For each subject with a clinically meaningful abnormality in vital signs, weight, or BMI (to be supplied by Sponsor), a table will be produced organized by parameter that lists each subject, age, sex, day of most abnormal value, the most abnormal value, and the reference range.

A listing of each subject's values will be created.

10.6. ECG

12-Lead ECGs data (PR, QRS, QT, QTcF, and HR) will be documented for subjects during study at baseline (Visit 1 and Visit 3), Day 43 (Visit 8), at End of Study (Visit 12) and at Cardiac Follow-up (Visit 14).

Analysis of Echocardiograms will be included in a separate report from ERT.

All ECG values will be presented in the subject data listing. In addition to the subject data listing with all ECG values, a listing of all abnormal, clinically relevant findings will be presented organized by subject, by parameter, then by visit.

10.7. Doppler Echocardiography

Color Doppler echocardiography (ECHO) will be conducted at a facility with experience for the subject's age at Screening, Maintenance period (Visit 8), End of study (Visit 12), and Cardiac Follow-up (Visit 14). ECHO 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 Cardiovascular SAP.

Results of ECHOs will be presented in a separate report from ERT.

10.8. Physical Examination

A complete physical examination will be performed at Screening Visit (Visit 1), day of randomization (visit 3) prior to first dose of study medication, and at the EOS visit. An abbreviated physical exam is performed at Day 15 (Visit 6), 43 (Visit 8), and 71 (Visit 10). A complete or abbreviated physical exam may be performed at the Cardiac follow-up visit for patients who do not enter the open-label extension study if clinically warranted.

All physical examination results will be presented in a subject data listing, including the description of abnormalities. New, clinically meaningful abnormalities will be reported as adverse events.

10.9. Neurological Examination

A complete neurological examination will be performed at Screening Visit (Visit 1) and EOS (Visit 13). An abbreviated neurological examination will be performed at randomization (visit 3) and at Visit 6.

Shift tables representing neurological exam results from randomization to EOS will be presented by body system.

All neurological examination results will be presented in a subject data listing, including the description of abnormalities.

10.10. Tanner Staging

Tanner Staging will be assessed for subjects >7 years old during the study at baseline period (Visit 3) and End of study (Visit 12). 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 onset and progress of pubertal changes will be recorded on a 5 point scale for boys and girls separately. Boys are rated for genital development and pubic hair growth through stage I to stage V. Girls are rated for breast development and pubic hair growth through stage I to stage V.

The number and percentage of subjects in each Tanner Stage will be presented for all visits by treatment group separately for boys and girls overall and also broken out for the following age groups:

>7 years to <=11,
>11 years to <=15,

>15 years to <=18.

All Tanner staging data will be presented in the subject data listing.

10.11. Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale data will be collected as per at screening visit (Visit 1), at randomization (visit 3), Titration period (at visit 6), maintenance period (at Visit 8 and 10) and at End of study visit (Visit 12).

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.

All individual subject C-SSRS data will be listed.

Suicidal Ideation:

The following outcomes are C-SSRS categories for suicidal ideation and have binary responses (yes/no):

Category	Outcome Description
[redacted]	[redacted]

Suicidal ideation is assessed as a "yes" answer at any time during the T + M period to any one of the five questions (1-5) above. The number and percentage of subjects with suicidal ideation will be presented, as well as the number and percentage having a "yes" response to each category (1-5) at least once during the T + M period. The denominator will be the number of subjects completing the C-SSRS at least once during the T + M Treatment period.

Suicidal Behavior:

The following outcomes are C-SSRS categories for suicidal behavior and have binary responses (yes/no):

Category	Outcome Description
[redacted]	[redacted]

Suicidal behavior is assessed as a "yes" answer at any time during the T + M period to any one of the five questions (6-10) above. The number and percentage of subjects who had suicidal behavior, as well as the number and percentage having a "yes" response to each category (6-10) at least once during the T + M period. The denominator will be the number of subjects completing the C-SSRS at least once during the T + M period.

Suicidal Ideation or Behavior:

An overall composite will be provided similar to the suicidal ideation and behavior endpoints, but will instead count a subject if any of the C-SSRS questions 1 through 10 are marked as 'yes' anytime during the T+M period.

Self-injurious behavior without suicidal intent:

The number and percentage of subjects having reported anytime during the T+M period experiencing a 'Self-injurious behavior without suicidal intent' event (Question 11) will be provided.

10.12. Brief Rating Inventory of Executive Function (BRIEF and BRIEF-P)

The Behavior Rating Inventory of Executive Function (BRIEF™) and its preschool version, BRIEF-P, are standardized, validated rating scales to measure executive function in children within the home and school environments that will be assessed by the parent according to the schedule in Table 1 (i.e. at Randomization (Visit 3), at Maintenance period (Visit 8) and at End of study visit (Visit 12)).

The BRIEF measures multiple aspects of executive functioning; scales include Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor.

The original BRIEF was the basis for the development of the BRIEF-P. The BRIEF-P Rating Form consists of 63 items that measure various aspects of executive functioning: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize.

For the BRIEF and the BRIEF-P, mean scores at Baseline, End of Study/ET and mean change from baseline to End of Study/ET, and descriptive statistics will be presented by treatment group for the Safety population (SAF).

11. Interim Analyses

No formal interim analysis is planned for Study 2.

Unblinding for Study 2 will not occur until data cleaning is completed and all decisions regarding protocol deviations warranting exclusion from the per protocol population have been made.

12. Changes from Analysis Planned in Protocol

- The 1501 and 1502 protocols set a target that 40% of enrolled subjects to be less than 6 years old, but candidate subjects have been older than expected. Consequently, the enrollment target has been revised to ensure that at least 25% of subjects are less than 6 years old.
- Protocols 1501 and 1502 state that efficacy and safety endpoints will be repeated separately for the titration and maintenance periods, however this is not planned to be conducted –Data from the T+M Period will be summarized and analyzed for all endpoints, and separate analyses of titration or maintenance periods will be generated only for selected endpoints.
- Protocols 1501 and 1502 state that analyses of safety data will be presented by treatment actually received. However, safety data will be presented by randomized treatment group except where noted otherwise.
- Protocols 1501 and 1502 provide sample size calculations to support a total study sample of 105 subjects, 35 per treatment group. A revised sample size calculation has increased the sample size to 40 subjects per treatment group, for a total of approximately120 subjects.
- Protocols 1501 and 1502 state that a sensitivity analysis for the primary efficacy endpoint will be conducted by adding a factor indicating whether a subject had a change in prescribed dose or type of concomitant AED medication during the T+M Period, however this is not planned to be conducted. Instead it is planned to compare the treatment groups with respect to the proportion of subjects who changed dose and/or type of AED concomitant medication during the T+M Period.
- Protocols 1501 and 1502 state that the longest interval between convulsive seizures will be analyzed using a log-rank test. However, further considerations of this endpoint suggest that while the first seizure-free interval may be subject to independent censoring, the second and later seizure-free intervals are subject to dependent censoring. Moreover, the last seizure-free interval is subject to intercept sampling, hence a longer seizure-free interval is more likely to be censored. Finally, the number of seizures or seizure-free intervals is informative about the underlying distribution, as subjects at a higher risk of experiencing recurrent events are likely to have shorter and hence more seizure-free intervals during the 84 day treatment period. Thus, a simple analysis comparing medians of the largest seizure free intervals was proposed.
- Responder analyses – Protocols 1501 and 1502 include a ≥40% response analysis as one of the key secondary endpoints. It was decided to not include this endpoint as the ≥50% response analysis is considered clinically meaningful.
- An analysis of the percentage of subjects who achieve a 25% reduction in seizures was added. The number of subjects whose seizures worsen during the study will be included, along with the percentage of worsening.
- The Protocol states that the BRIEF rating scale will be used to evaluate cognition in children aged 2-18. The BRIEF-P will be used for children aged 2-4, and the BRIEF will evaluate children aged 5-18.
- The protocol included the exploratory objective to compare the ZX008 0.2 mg/kg/day and ZX008 0.8 mg/kg/day doses on primary , secondary, safety, and PK endpoints. Comparisons between doses were not made using inferential statistics.
- The protocol states that subjects will enter information daily into the diary; in some cases, data could not be entered directly into the diary and had to be entered via the DCR process. These data were analyzed in the same manner as data entered directly.
- An analysis of the percentage of subjects who achieve a 100% reduction (near seizure-free) in seizures was added. The number of subjects whose seizures worsen during the study will be included, along with the percentage of worsening.
- Intermediate missing day and post-discontinuation imputation was added: Intermediate missing days should be imputed as the worse observed outcome for that patient if the patient was assigned to an active arm or zero seizures if the patient was assigned to placebo.
  For patients who discontinued the study, the day of discontinuation should be imputed as the worse observed outcome if assigned to ZX008 and as zero counts if the patient was assigned to placebo. The remaining days should be imputed using the baseline seizure counts for all arms.

- Impute the number of siezures in an uncountable cluster was added. Such an impuatation is necessary to make it possible to calculate seizure frequency. For cluster seizures that were reported as uncountable, the assigned number of seizures in the cluster is assigned as 3.

13. Programming Considerations

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. General Considerations

- One SAS program can create several outputs. / A separate SAS program will be created for each output.
- One output file can contain several outputs. / Each output will be stored in a separate file.
- Output files will be delivered in Word format / pdf format.
- Numbering of TLFs will follow ICH E3 guidance.

13.2. Table, Listing, and Figure Format

13.2.1. General

- All TFLs will be produced in landscape format, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:
- <Sponsor Name> Protocol <XXX> (Syneos Health study number <xxx>)

- Draft/Final Run <date>
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each FL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

13.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include “unit” in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;

- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

13.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. Every p-value less than 0.0001 will be presented as <0.0010. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.9999, then present as >0.9999.
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for

the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.

- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available

13.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907) .

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output."

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STATISTICAL ANALYSIS PLAN FOR CARDIOVASCULAR ENDPOINTS

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
Investigational Product:	ZX008
Sponsor Study No.:	ZX008-1501 and ZX008-1502; "Study 2"
SAP Status:	V1.0
Date of SAP:	09Jun2020
SAP Prepared by:	ERT
Sponsor:	Zogenix International Limited A subsidiary of Zogenix, Inc. 5858 Horton Street, Suite 455 Emeryville, CA 94608 USA

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Table of Contents

Abbreviations and Definitions of Terms

ΔΔQTcF	Change from baseline and placebo (Double-Delta) in QTcF
ACI	Abnormal Clinically Insignificant
ANOVA	Analysis of Variance
APCS	Abnormal Potentially Clinically Significant
bpm	Beats per minute
C_{max}	Maximum Plasma Concentration
CI	Confidence Interval
CL/F	Oral dose apparent clearance
DS	Dravet's Syndrome
ECG	Electrocardiogram
E_{max}	Maximum Effect
GSMB	Global Superimposed Median Beat
kg	Kilogram
h, hr	Hour
HR	Heart Rate
m	Minutes
mg	Milligram
mL	Milliliter
mm	Millimeter(s)
mmHg	Millimeters of Mercury
ms	Millisecond(s)
N	Sample Size
ng	Nanogram
PAH	Pulmonary Arterial Hypertension
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PR	Interval between the start of the P wave and start of the Q wave
QRS	QRS waves complex on the electrocardiogram tracing
QT	Interval between the start of the Q wave and the end of the T wave
QTc	Corrected QT duration
QTcF	QT interval corrected using Fridericia's formula
RR	The time interval between consecutive heart beats.
SAP	Statistical Analysis Plan
SD	Standard Deviation

s	Second(s)
SMEI	Severe Monoclonal Epilepsy of Infancy
SUPED	Sudden Infant Death in Epilepsy
t_{max}	Time to maximum concentration (C_{max})
$t_{1/2}$	Half-life associated with terminal phase of the concentration-time profile
TdP	Torsade de Pointes
ZX008	Fenfluramine Hydrochloride

1. Introduction

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. Cognitive 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 (Shorvon2011), 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 usually live in institutional care homes.

The primary known pharmacologic action of fenfluramine is serotonin release in the CNS (Baumann, 2014); preliminary evidence suggests a role for other mechanisms of action as well. Fenfluramine is readily absorbed after oral administration with an oral bioavailability of 60-70% (Bever and Perry, 1997) and a Tmax of 4 hours (Beckett & Brookes, 1967). Terminal half-life (t1/2) is approximately 20 hours for the parent and 30 hours for the active metabolite, norfenfluramine. Metabolism occurs primarily by Cytochrome P450 (CYP)1A2, CYP2B6 and CYP2D6. CYP2C9, CYP2C19 and CYP3A4 also appear to be involved, but to a lesser degree. Elimination of the drug and its metabolites is largely renal. The drug readily crosses the blood brain barrier and is widely distributed in all tissues.

When fenfluramine was marketed for treatment of obesity at doses of 60-120 mg/day, reports of cardiac valvular disease emerged (Connolly, 1997). The FDA issued an advisory request for information from similar cases and eventually requested voluntary withdrawal of fenfluramine and dexfenfluramine from the market in 1997. There were 144 individuals reported to have valvulopathy involving fenfluramine or dexfenfluramine in the initial 1997 communication (CDC, 1997). Of 113 confirmed cases, 111 occurred among women; the median age was 44 years (range: 22-68 years). Of these 113 cases, 2 (2%) used fenfluramine alone; 16 (14%) dexfenfluramine alone; 89 (79%) a combination of fenfluramine and phentermine; and 6 (5%) a combination of all 3 drugs. The median duration of drug use was 9 months (range: 1-39 months). Overall, 87 (77%) of the 113 cases were symptomatic and 24 (27%) required valve replacements.

The prevalence of valve lesions was assessed for patients who were exposed to these drugs but who had no obvious history of cardiac disease or cardiac symptoms in 5 independent unpublished echocardiographic surveys submitted to FDA in 1997. These surveys demonstrated a prevalence of valvular disease meeting the case definition ranging from 30.0% to 38.3% (overall: 32.8%; 95% confidence interval=27.7%-38.9%). However, subsequent studies sought to estimate the risk of valvulopathy in fenfluramine-treated adult obese patients and found fenfluramine-associated valvular disease was less common than the original observational reports suggested, approximately 9.6% for aortic valve dysfunction (range 5.0% to 26.3%) and 3.1% for mitral regurgitation of mild severity or greater (Loke, 2002; Sachdev, 2002).

In 1981, a report was published describing 2 patients who developed pulmonary hypertension while taking fenfluramine (Douglas, 1981). Additional rare cases, some of which were severe or even fatal, were reported subsequently (McMurray, 1986; Pouwels, 1990).

Zogenix has evaluated the effect of multiple oral administrations of therapeutic (30 mg/day, ie, 15 mg BID) and supratherapeutic (120 mg/day, ie, 60 mg BID) doses of ZX008 on the heart rate corrected QT interval using Fridericia's formula (QTcF) in healthy adult volunteers (Study 1603). The supratherapeutic ZX008 dose of 120 mg/day provided a 4-fold higher dose than the maximum dose planned for clinical use, while maintaining a reasonable safety margin. This study demonstrated that there is no significant effect of ZX008 on QTc intervals at either the therapeutic or supratherapeutic dose; multiple therapeutic and supratherapeutic doses of ZX008 do

not prolong QTcF intervals. Following multiple doses of 15 mg and 60 mg ZX008, trough levels of fenfluramine and norfenfluramine indicated that steady state was effectively reached prior to the end of the 7-day interval Zogenix has reported safety and efficacy data from 2 adequate and well controlled studies, Study 1 and Study 1504 Cohort 2, and 1 interim analysis from the open-label extension study (Study 1503). Study 1 represents the first 119 subjects randomized in two identical and parallel studies, 1501 and 1502, and compared 2 doses of ZX008, 0.2 mg/kg/day and 0.8 mg/kg/day (up to a maximum of 30 mg/day), to placebo in subjects receiving standard of care anti-epileptic treatments excluding stiripentol (STP). Study 1504 Cohort 2 compared a dose of ZX008 0.5 mg/kg/day (up to a maximum of 20 mg/day) to placebo in subjects receiving standard of care anti-epileptic treatments where administration of STP (in combination with clobazam [CLB] and/or valproate [VPA]; i.e., the STP regimen) was mandatory. A prospectively-defined cardiovascular monitoring program that employed color Doppler echocardiography (ECHO) and electrocardiograms was implemented in the ZX008 clinical program (all Dravet syndrome trials) to monitor for valvular heart disease (VHD) or pulmonary artery hypertension (PAH); this ECHO program was designed with input from FDA and from cardiology experts. As of the writing of this Statistical Analysis Plan, no study subject in the entire ZX008 program, has developed VHD or PAH.

This Statistical Analysis Plan (SAP) for Cardiovascular Endpoints outlines the planned analyses to support the assessment of electrocardiographic (ECG) and echocardiographic data in the Study 2 clinical study report. Study 2 represents all subjects enrolled in Study 1501 and 1502 who were not included in Study 1. The planned analyses identified in this SAP may be included in regulatory submissions, and exploratory analyses not defined in this SAP may be performed to support a more thorough understanding of the safety data. All post-hoc or unplanned analyses performed not identified in this SAP will be documented.

Documents used to develop this SAP are:

- Study Protocol ZX008-1501 (Amendment 3.0, 31-October-2016).
- Study Protocol ZX008-1502 (Amendment 2.4.3, 07-February-2019).
- Study 1 Statistical Analysis Plan (Version 2.1, 17-September-2017).
- CAMI 7 12-Lead Analysis Plan for use with Eli 150c (Inventive Health/Zogenix) (Version 1.0, 11-January-2016).
- ZX008 Investigational Brochure (Version 7, 31-July-2019).

2. Study Design and Cardiovascular Analysis Objectives

2.1 General Design and Plan

Study 2 contains pooled data from two studies, 1501 and 1502. Both studies are multicenter, randomized, double-blind, parallel group, placebo-controlled trials of two fixed doses of ZX008 (Fenfluramine Hydrochloride) oral solution as adjunctive therapy in children and young adults with Dravet syndrome. The first 119 subjects randomized were reported as Study 1; Study 2 represents all subjects enrolled in Study 1501 and 1502 who were not included in Study 1.

Each subject is assigned to one of 2 treatments (0.2 mg/kg or 0.8 mg/kg) or placebo.Treatments were assigned on a 1:1:1 basis.

Electrocardiograms (ECGs) and echocardiograms (ECHOs) are being analyzed by ERT (formerly Biomedical Systems (St. Louis, MO)).

All ECGs were reviewed and interpreted by a board-certified cardiologist. Echocardiograms were reviewed by two, board-certified cardiologists. In the case of a discrepancy between the readers, the echocardiogram was sent to adjudicators for final reading. At the initiation of the ZX008 Program, the International (Pediatric) Cardiology Advisory Board (ICAB) was set-up to oversee the vendor's ECHO readings. ICAB members were chosen solely based on their academic credentials and experience, with the Chair being chosen based upon his/her seniority and respect in the field of echocardiography. When there was a differing interpretation of findings in an ECHO of any subject between the vendor and ICAB (either in the alert level of valvular regurgitation or presence or absence of pulmonary hypertension), the following process occurred: a telephone conference call was to be held with the vendor ERT cardiology readers and ICAB reader and ICAB Chair (if the

Chair was reader,then only he/she will be on call) to discuss the ECHO findings and try to come to an agreement on interpretation; if agreement could not be reached then ICAB Chair read the ECHO and his/her reading become the official reading. This one ECHO report was then be sent to the IDSMC.

2.2 Objectives

The primary objective of Study 2 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). Safety endpoints of the study include the assessment for cardiac toxicity as demonstrated by ECG and ECHO.

2.2.1. Cardiovascular Safety Objectives

The primary cardiovascular safety objective of this analysis is to evaluate the effect of ZX008 on the heart as demonstrated by both the 12-lead ECG and ECHO.

Variables included in the analysis are listed below. These will be compared between Placebo and the 0.2 mg/kg and 0.8 mg/kg groups independently.

2.3 Endpoints

2.3.1 ECG

The change from baseline will be calculated and compared between placebo and the two dosing groups (0.2 mg/kg and 0.8 mg/kg) for the main and secondary ECG endpoints for each of the variables and subgroups listed.

2.3.1.1 Main Focus of ECG Analysis

The main focus for ECG will be the mean change between measurements of QT interval corrected using Fridericia's formula (QTcF) for ZX008 and placebo after baseline adjustment, (ΔΔQTcF), calculating the upper bound of the one-sided 95% confidence interval.

2.3.1.2 Other ECG Analyses

Other secondary endpoints that will be presented by dose and subgroups are:

- Mean QTcF duration including changes from baseline (ΔQTcF)
- Mean QRS duration (including changes from baseline (ΔQRS) and from placebo and baseline (ΔΔQRS)
- Mean PR interval measurements (including changes from baseline (ΔPR) and from placebo and baseline (ΔΔPR)
- Mean Heart rate (including changes from baseline (ΔHR) and from placebo and baseline (ΔΔHR)
- Categorical analyses for each variable and subgroup listed below:
    - QTcF (number and percentage of subjects, by dose)

Age	Gender	Values
0 to < 12 years	Males and Females	< 320 ms
		≥ 320ms to ≤ 450 ms
		> 450 ms to ≤480 ms
		> 480 ms
12 to 18 years	Males	< 320 ms
		≥ 320 ms to ≤ 450 ms
		> 450 ms to 500 ms
		> 500 ms
12 to 18 years	Females	< 320 ms
		≥ 320 ms to ≤ 470 ms
		> 470 ms to≤ 500 ms
		> 500 ms

- For all ages QTcF changes from baseline (number and percentage of subjects, by dose)
  - ≤ 30 ms
  - > 30 ms to ≤ 60 ms
  - > 60 ms
- QRS (number and percentage of subjects, by dose)

Age	Gender	Values
2 to <6 years	Males and Females	≤ 90 ms
		>90ms to ≤100ms
		> 100 ms
		≤ 100 ms
6 to < 12 years	Males and Females	> 100 ms to ≤ 110 ms
		> 110 ms
		≤110ms
		>110 ms to ≤ 120ms
12 to 18 years	Males and Females	>120ms
		≤ 90 ms

- PR (number and percentage of subjects, by dose)

Age	Gender	Values
2 to <6 years	Males and Females	≤ 90 ms
		> 90ms to ≤ 150 ms
		>150 ms
6 to < 12 years	Males and Females	≤ 100 ms
		> 100 ms to ≤ 170 ms
		>170 ms
12 to 17 years	Males and Females	≤110ms
		>110 ms to ≤ 180ms
		>180ms
18 years	Males and Females	≤120 ms
		>120 ms to ≤ 220ms
		>220 ms

- Heart rate (number and percentage of subjects, by dose)

Age	Gender	Values
2 to <6 years	Males and Females	<80 bpm
		≥80 bpm to ≤140bpm
		> 140 bpm to ≤ 180 bpm
		> 180 bpm Increase or decrease from baseline > 20 bpm
6 to < 12 years	Males and Females	<60 bpm
		≥60 bpm to ≤120bpm
		> 120 bpm to ≤ 150 bpm
		> 150 bpm Increase or decrease from baseline > 20 bpm
12 to 18 years	Males and Females	< 50 bpm
		≥50 bpm to ≤100bpm
		> 100 bpm to ≤ 150 bpm

		> 150 bpm Increase or decrease from baseline > 20 bpm

- Overall characterization of normal and abnormal ECGs and the number and percentage of subjects with normal and abnormal ECGs. ECGs will be characterized as Normal, Abnormal Clinically Insignificant (ACI), or Abnormal Potentially Clinically Significant (APCS). The number and percentage of ECGs within each category will be calculated by dose.
- Number and percentage of subjects that develop abnormalities of repolarization on treatment, as manifest by new ST and T wave abnormalities. The number and percentage of ECGs within each category will be calculated by dose.

Analysis for specific arrhythmias: Torsade de Pointes (TdP), ventricular tachycardia/fibrillation, atrial fibrillation/flutter, supraventricular tachycardia, etc., including associations between specific ECG findings and selected clinical adverse events of interest will be explored as appropriate (events that may signal pro-arrhythmia: syncope, palpitations, dizziness, tachycardia, etc.). Shift tables will be constructed for arrhythmias.

2.3.1.3 Listing for Abnormalities

Listings for ECG abnormalities by dosing, subject, and time-point will be provided for the following:

- Heart Rates
- PR-Interval
- QRS Duration
- QT-Interval
- First degree AV-Block
- Second degree AV-Block (Type 1)
- Second degree AV-Block (Type 2)
- Third-degree (complete) AV-Block

2.3.2 Echocardiograms

2.3.2.1 Main Focus for Echocardiograms

The main focus for the echocardiographic analysis is the regurgitation score for the mitral and aortic valves at each time-point with the main focus being the development of clinically meaningful (pathologic) changes in valve regurgitation (definitions and thresholds defined below).

- Number of subjects who meet the FDA case definition of drug associated valvulopathy-aortic regurgitation ≥ mild and/or mitral regurgitation ≥ moderate
- Number of subjects with ≥ trace mitral or aortic regurgitation at least one time post-baseline
- Number of subjects with ≥ trace mitral or aortic regurgitation at end of study
- Number of subjects within each mitral or aortic regurgitation score by visit
- Number of subjects with clinically confirmed Valvular heart disease (VHD)

2.3.2.2 Other Echocardiographic Analysis

Other, secondary endpoints include:

- Number of subjects within each tricuspid or pulmonic regurgitation score by visit
- Number of subjects with normal or trace tricuspid or pulmonic regurgitation at baseline and ≥ mild tricuspid or pulmonic regurgitation at end of study
- Pulmonary Artery Systolic Pressure (PASP)
  - Mean change from baseline at end of study
  - Mean maximum change from baseline at anytime during therapy
  - Number of subjects with change from baseline at anytime during therapy:
    - > 10 mmHg

- >15 mmHg
- >20 mmHg

- Number of subjects with PASP>35 mmHg at anytime during therapy

- Right ventricular outflow tract (RVOT) acceleration time (will be used only as confirmatory variables for pulmonary hypertension)
  - Mean Change from Baseline in RVOT (msec) by visit
  - Number of subjects with Baseline ≥100 msec and at EOS/ET RVOT <100 msec
  - Number of subjects with any RVOT measurement < 100 msec post-baseline

Summary of the number of ECHOs per subject will also be presented.

2.3.2.3 Heat Maps

Heat maps will be constructed for all valve scores to visualize longitudinal changes, if any, in regurgitation measures in individual subjects over time. An example of a heat map is shown below.

Dosing	Subjects	Visit 1	Visit 8	Visit 12
Placebo	2 subjects	Absent	Absent	ECHO
Placebo	5 subjects	Absent	Trace	Trace
Placebo	1 subject	Absent	Mild	Trace
ZX008 0.2 mg/kg/day	4 subjects	Absent	Absent	Absent
….				

Note: different colors represent the valve scores such as No ECHO, Absent, Absent, Mild, Moderate, and Severe.

2.4 Study Population

Male and female subjects, aged 2 to 18 years of age with a medical history and clinical diagnosis of Dravet syndrome who meet other eligibility criteria could be enrolled in the study. This section includes the inclusion and exclusion criteria related to cardiac safety.

2.4.1 Inclusion Criteria Related to Cardiac Safety

No inclusion criteria were related to cardiac safety.

2.4.2 Exclusion Criteria Related to Cardiac Safety

Subjects must not meet any of the following criteria to be eligible for study participation:

- Subject has Pulmonary Arterial Hypertension (PAH)
- Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke.
- Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoaminoxidase 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. (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)
- 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.

2.4.3 Sample Size

No formal sample size calculations were conducted related to cardiac safety for Study 2. Study 2 includes all subjects enrolled in ZX008-1501 and ZX008-1502 except the first 119 subjects which comprise Study 1.

2.5 Randomization and Blinding

Each subject was randomized in a 1:1:1 fashion and receive one of the following treatments:

A. 0.2 mg/kg/day ZX008
B. 0.8 mg/kg/day (up to 30 mg/day) ZX008
C. Placebo

Neither the subjects nor the investigator knew which treatment is being administered.

3. Cardiac Safety Data Collection and Analysis

3.1 ECG Assessment

3.1.1 Equipment

Twelve-Lead Electrocardiograms were collected on a Mortara ELI-150c ECG machine (Milwaukee, WI) located at each clinical site.

3.1.2 Transfer of ECGs

Electrocardiograms were digitally transferred to ERT for analysis.

3.1.3 Collection of ECGs

The clinical ECG database will be derived from 12-lead ECGs collected from the ELI-150c ECG machines.

Single, 12-lead ECGs were collected at Screening, Baseline (Visit 3), Week 6 (Visit 8), and Week 14 (Visit 12). ECGs were collected after the subjects had been in supine position resting for ≥5 minutes.

The time of the ECG was not controlled.

3.1.4 Definition of Baseline

The baseline for this study will be the data collected from the ECG taken at Baseline (Visit 3).

3.1.5 Variables Measured

At the central laboratory, using CAMI software (or equivalent), the cardiac technician will annotate the Global Superimposed Median Beat (GSMB).

The following variables will be measured or calculated on each ECG:

- QRS duration
- PR interval
- Heart rate (10 second average)
- QT
  - The QT interval will be measured from the earliest detection of depolarization in any lead (beginning of the Q or R wave) to the latest detection of repolarization in any lead (end of the T-wave).
- QTcF

The RR interval will be reported, from which the corrected QT interval (QTc) using Fridericia's formula (QTcF) will be calculated.

Fridericia's correction: $QTcF = \frac{QT}{RR^{1/3}}$ where QT, RR, and QTcF are expressed in seconds.

For convenience, QT, RR, PR, QRS, andQTcFwill be shown in milliseconds (ms) in the tables, figures and listings.

3.1.6 Clinical Analysis of ECGs

The over-reading cardiologist will give a clinical interpretation for each ECG at each time point. These will be presented in the data listing provided at the end of the study. Each ECG will be classified as Normal (N), Abnormal Clinically Insignificant (ACI), or Abnormal Potentially Clinically Significant (APCS).

3.1.7 Non-Digital ECG Evaluation

Data not acquired using the ECG equipment provided by ERT will not be eligible for centralized reading, nor will it be included in the database.

3.2 Echocardiographic Analysis

3.2.1 Equipment

Site-owned equipment was used for the collection of echocardiograms.

Prior to being qualified for subject enrollment, all echocardiographers were required to participate in a WebEx PowerPoint training presentation and transferred test data to BMS. The WebEx session consisted of reviewing protocol specific views, study related forms and the process of uploading the images through web portal.

Each echocardiographer was required to submit a certification ECHO. The certification ECHO was performed on a non-study participant. The participating ECHO facility was informed during the training session that they would not be able to perform ECHOs on true study subjects until they received a "passed" Certification ECHO Evaluation Form.

3.2.2 Transfer of Echocardiograms

Electrocardiograms were either digitally transferred or copied to CD and sent via courier to ERT for analysis.

3.2.3 Collection of Echocardiograms

ECHOs were taken at Screening, Week 6 (Visit 8), and Week 14 (Visit 12). For each ECHO, cardiac technicians check to make sure the Nyquist Limit (color scale) was set between 60 cm/s and 80 cm/s. All sonographers at the study sites submitted a certification ECHO before study ECHOs were obtained.

The time of the ECHO was not controlled.

3.2.4 Definition of Baseline

The baseline for this study will be the data collected from the ECHO taken at Screening.

3.2.5 Variables Measured

Echocardiograms were evaluated by two cardiologists using DigiView software. Details of the assessment and adjudication process are available in the ECHO operations manual for these studies.

In addition to assessing each valve (Mitral, Aortic, Tricuspid, and Pulmonary) for regurgitation, the following variables were measured or calculated on each ECHO:

- Right Ventricular Outflow Tract Acceleration Tim (RVOT)
- Pulmonary Artery Systolic Pressure (PASP)
- Pulmonic Valve Peak Regurgitation Jet Velocity (PVPR)

3.2.6 Clinical Analysis of ECHOs

Each ECHO was read, independently by two physicians. A third physician was assigned as an adjudicator. The adjudicator read the ECHO if the any of the following discrepancies occurred between the first and second reader:

- Aortic valve findings were not identical
- Mitral valve findings were not identical
- LVFS difference between the two physicians was >5%
- LVEF difference between the two physicians was >10%

- PASP difference between the two physicians was >10 mmHg
- Clinical significance between the two readers was not identical

The adjudicator chose which of the two readings was the final reading.

3.2.7 Alert Criteria

Echocardiographic alert criteria included:

- Valve regurgitation (aortic or mitral)
- ≥ moderate valve regurgitation (tricuspid or pulmonic)
- Mean mitral valve gradient ≥ 4 mmHg
- Mean aortic valve gradient ≥ 15 mmHg
- Mean tricuspid valve gradient ≥ 4 mmHg
- Peak pulmonic valve gradient ≥ 21 mmHg
- Tricuspid regurgitation jet velocity > 2.8 meters/sec with orwithout the findings OR
- One of the following findings in the absence of being able to measure tricuspid regurgitation jet velocity:
  - Change in right ventricle/left ventricle basal diameter ratio > 1.0
  - Right ventricular outflow tract flow acceleration time < 100 msec
  - Dilation of the inferior cava vein (diameter > 21mm and <50% inspiratory collapse) and/or right atrial dilatation
  - Change in the geometry of the interventricular septum in systole (flattening) with left ventricular eccentricity index >1.1 in systole and/or in diastole
  - Early diastolic pulmonary regurgitation velocity > 2.2 m/sec
  - Tricuspid Annular Plane Systolic Excursion below 18 mm or below Z-score – 2

4. Statistical Analysis

The statistical analyses of the cardiac safety data are designed to assess the potential toxicity of ZX008 when administered for up to 14 weeks as adjunctive treatment for children and young adults with Dravet syndrome.

4.1 General Principles and Considerations

This section describes the algorithms and conventions that will generally apply to program analyses and to the formatting of the data, as required to perform the proposed summary tabulations and to create the individual subject data listings. Unless otherwise indicated, these specifications will apply to all analyses. For details on the tables and figures that will be created, please refer to Section 5, Tables, Figures, and Listings.

The statistical analysis will be reported using summary tables, figures, and data listings.

ECG and ECHO variables at each time point will be obtained. Changes from baseline will be calculated and compared for each of 0.2 and 0.8 mg/kg/day treatment groups to placebo. The primary outcome is the assessment for the development of valvular heart disease and pulmonary arterial hypertension.

Continuous variables will be summarized using descriptive statistics (i.e., total number [n], mean, standard deviation [SD], minimum, maximum, and 95% CI). Results will be presented to one or two decimal places for means and SD, as appropriate.

Qualitative variables will be presented as category counts and percentages. Percentages will be presented to one decimal place.

All dates will be displayed in DDMMMYYYY format (e.g.,15DEC2012).

All analyses will be carried out using SAS® Version 9.4 or higher.

4.2 Analysis Population

ECG and ECHO data will be analyzed using a Safety Population, including all randomized subjects who received at least one dose of study medication in Study 2, excluding the 119 subjects in Study 1.

As there are few subjects per site, no comparisons between sites will be conducted.

4.2.1 Handling of Missing Data

All data available will be used for the analysis. Missing data points will not exclude the rest of the subject's data from analysis, and missing data will not be imputed.

4.3 Interim Analysis

No interim analysis is scheduled for this trial.

4.4 Multiplicity Adjustments

No adjustments for multiplicity will be made for the primary cardiovascular endpoint.

4.5 Primary Analyses

4.5.1 Electrocardiogram

The primary ECG objective is to evaluate the effect of ZX008 0.8 mg/kg/day (max 30 mg/day) on QTcF.

The primary analysis of the QTcF is the mean baseline-adjusted difference between treatment and placebo and will be performed using an analysis of variance (ANOVA) for each post-dose time point. The ANOVA model will include a fixed effect for treatment. The upper bound of the one-sided 95% CI (or, equivalently, two-sided 90% CI) of the mean baseline-adjusted difference between treatment and placebo QTcF (ΔΔQTcF) will be calculated from the ANOVA for each time point.

The general formula to calculate the ΔΔQTcF at the *i*th timepoint is:

Mean ΔΔQTcF*i* = Mean ΔQTcF*i* for the active group - Mean ΔQTcF*i* for the placebo group, based on the ANOVA model, where *i* = at *i*th timepoint and ΔQTcF*ti* =QTcF*ti*on Day 1 –QtcF*ti* at Baseline (i.e., Day -1), where *ti* = at *i*th time point for subject t

4.5.2 Echocardiogram

The primary ECHO objective is to evaluate the effect of ZX008 0.8 mg/kg/day (max 30 mg/day)on the mitral and aortic valves, and in particular evaluating for the development of VHD and PAH.

The number and percentage of subjects with each category of valvular regurgitation will be calculated by regimen and visit for each valve (Mitral, Aortic, Tricuspid, and Pulmonary), based on age (where appropriate.

PASP will be analyzed for mean, mean maximum change from baseline at each time point, as well as changes in PASP compared to baseline using 5, 10 and 15 mmHg differences. Abnormal values will be categorized by regimen and visit.

The primary analysis of the mitral and aortic valves is the change from baseline in regurgitation category between treatment and placebo and will be performed using an ANOVA model with effect for treatment.

4.6 Secondary Analyses

Analyses conducted with 0.8 mg/kg/day (max 30 mg/day) ZX008 will be conducted with 0.2 mg/kg/day ZX008. Central tendency analyses will be conducted to include per-visit data and changes from baseline and placebo for the ECG and ECHO values for all subjects. The variables for analysis are listed in sections 2.3.1.2 and 2.3.2.2.

4.7 Additional Analysis

Additional analysis may be used, as appropriate.

4.8 Categorical Analysis

Categorical data will be reported as both numbers and percentages and will include changes from baseline in both ECG and ECHO variables.

5. Tables, Figures, and Listings

Number	Title
Table 1.1.1	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Males and Females, 0 to <12 Years
Table 1.1.2	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Males, 12 to 18 Years
Table 1.1.3	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Females, 12 to 18 Years
Table 1.1.4	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Males, 0 to <12 Years
Table 1.1.5	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Females, 0 to <12 Years
Table 1.2.1	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - Heart Rate, Safety Population - Males and Females, 2 to < 6 Years
Table 1.2.2	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - Heart Rate, Safety Population - Males and Females, 6 to < 12 Years
Table 1.2.3	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - Heart Rate, Safety Population - Males and Females, 12 to 18 Years
Table 1.3.1	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QRS Duration, Safety Population - Males and Females, 2 to < 6 Years
Table 1.3.2	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QRS Duration, Safety Population - Males and Females, 6 to < 12 Years
Table 1.3.3	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QRS Duration, Safety Population - Males and Females, 12 to 17 Years
Table 1.3.4	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QRS Duration, Safety Population - Males and Females, 18 Years
Table 1.4.1	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - PR-Interval, Safety Population - Males and Females, 2 to < 6 Years
Table 1.4.2	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - PR-Interval, Safety Population - Males and Females, 6 to < 12 Years
Table 1.4.3	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - PR-Interval, Safety Population - Males and Females, 12 to 17 Years
Table 1.4.4	Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - PR-Interval, Safety Population - Males and Females, 18 Years
Table 1.5	Means, Mean Differences from Baseline, and Mean Differences from Placebo and Baseline for ECG Data - QT-Interval, Safety Population
Table 2.1.1	Categorical Summary of ECG Data - QTcF, Safety Population - Males and Females, 0 to <12 Years
Table 2.1.2	Categorical Summary of ECG Data - QTcF, Safety Population - Males, 12 to 18 Years
Table 2.1.3	Categorical Summary of ECG Data - QTcF, Safety Population - Females, 12 to 18 Years
Table 2.1.4	Categorical Summary for ECG Data - QTcF Change from Baseline, Safety Population - Males and Females, 0 to <12 Years
Table 2.1.5	Categorical Summary for ECG Data - QTcF Change from Baseline, Safety Population - Males, 12 to 18 Years
Table 2.1.6	Categorical Summary for ECG Data - QTcF Change from Baseline, Safety Population - Females, 12 to 18 Years
Table 2.2.1	Categorical Summary of ECG Data - Heart Rate and Change from Baseline, Safety Population - Males and Females, 2 to <6 Years

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REVISION HISTORY

Version	Date Effective	Originator	Comments
0.1	15APR2020	ERT	Note that this document was first drafted under Biomedical Systems, and Biomedical Systems is now ERT. 1. Replaced references to Biomedical Systems with ERT. 2. Revised formatting of Biomedical Systems document to ERT formatting and style.
1.0	27May2020	ERT	Final version.
1.0	09Jun2020	ERT	Corrected Anupam Agarwal's title on signature page.