16.1.9 Documentation of Statistical Methods

The documents listed below are provided on the following pages:

Statistical Analysis Plan – Cohort 2 (Protocol No: ZX008-1504) dated 25 June 2018

STATISTICAL ANALYSIS PLAN

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

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

Protocol No: ZX008-1504

Prepared by:
Francis Ruvuna
and Revised by:
Gosford A. Sawyerr
and Revised by:
Darren Hughes
inVentiv Health Clinical

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SIGNATURE PAGE

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Protocol No: ZX008-1504

• Gail Farfel	• 25 JUN 2018
Gail M. Farfel, PhD, **EVP, Chief Development Officer** **Zogenix International Limited**	**Approval Date**
•	•
Michael Lock, PhD **Consultant Statistician** **Zogenix International Limited**	**Approval Date**
• Darren Hughes	• 25 June 2018.
Darren Hughes **Principal Statistician** **inVentiv Health Clinical**	**Approval Date**

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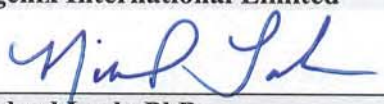
Gail M. Farfel, PhD, **EVP, Chief Development Officer** **Zogenix International Limited**	**Approval Date**
• 	• 25-JUN-2018
Michael Lock, PhD **Consultant Statistician** **Zogenix International Limited**	**Approval Date**
•	•
Darren Hughes **Principal Statistician** **inVentiv Health Clinical**	**Approval Date**

REVISION HISTORY

Statistical Analysis Plan DRAFT 1.0 Sanjay Mitter based on 8 February 2016 version (Protocol Amendment 2.0)

Statistical Analysis Plan DRAFT 2.0 Francis Ruvuna based on 29 December 2016 version (Protocol Amendment 2.3, Version 3.0)

Statistical Analysis Plan DRAFT 2.1 Gosford Sawyerr, based on 20 February 2017 version (Protocol Amendment 2.5)

Statistical Analysis Plan DRAFT 2.2 Darren Hughes, based on 10 July 2017 version (Protocol Amendment 2.5)

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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
CRU	Clinical Research Unit
DS	Dravet syndrome
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	electronic Case Report Form
EOS	End of study
EPAR	European Public Assessment Report
EQ-5D-5L	Standardized measure of health status
ET	Early Termination
FAS	Full Analysis Set
HR	Heart Rate
IDSMC	Independent Data and Safety Monitoring Committee
IMP	Investigational Medicinal Product
IPCAB	International Pediatric Cardiology Advisory Board
IR	Incidence rate
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	Minutes
mITT	modified Intent-to-Treat
mL	Milliliter
MMRM	Mixed Effects Model for Repeated Measures
msec	Millisecond
PedsQL	Pediatric Quality of Life Inventory

ABBREVATION	DEFINITION
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
QoL	Quality of Life
QOLCE	Quality of Life in Childhood Epilepsy
QTcF	corrected QT interval using Fredericia method
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SMEI	Severe Myoclonic Epilepsy Of Infancy
SOC	System Organ Class
T+M	Titration plus Maintenance Periods
TEAE	Treatment Emergent Adverse Event
THC	Tetrahydrocannabinol
TSH	Thyroid Stimulating Hormone
WHO-DD	World Health Organization Drug Dictionary
ZX008	Fenfluramine Hydrochloride Oral Solution

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). DS is a highly treatment-resistant and refractory epilepsy syndrome. The vast majority of patients who survive to adulthood are wholly dependent on around-the-clock caregivers and eventually live in institutional care homes. To date, only one treatment, Diacomit® (stiripentol) is approved, and only in Europe and Canada, as adjunctive therapy in patients with SMEI (Dravet syndrome), and must be co-administered with clobazam and valproate.

Zogenix has developed a new formulation of fenfluramine hydrochloride, ZX008, for the adjunctive treatment of DS. This study is two cohort study designed to assess the Pharmacokinetic and Safety Profile of Single Dose of ZX008 (Cohort 1), followed by a randomized, double-blind placebo-controlled Cohort 2 to assess the efficacy and safety of ZX008 compared to placebo in a cohort of patients taking stiripentol as one of their background AEDs. This statistical analysis plan presents a detailed plan of analyses of the Cohort 2 part of the study. Cohort 2 is designed to formally evaluate and provide evidence of the efficacy and safety of ZX008 versus Placebo.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary efficacy objective of this multicenter two-cohort study is related to the double-blind, placebo-controlled part of the study (Cohort 2):

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

2.2 KEY SECONDARY OBJECTIVES

The key secondary efficacy objectives of the study are related to the double-blind, placebo-controlled part of the study (Cohort 2), to demonstrate that ZX008 is superior to placebo on the following endpoints:

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

- The longest convulsive seizure-free interval.

2.3 ADDITIONAL SECONDARY OBJECTIVES

Additional secondary efficacy objectives of the study (Cohort 2) are to demonstrate that ZX008 is superior to placebo on the following endpoints:

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

2.4 SAFETY OBJECTIVE

The safety objectives of the study are:

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

2.5 PHARMACOKINETIC OBJECTIVE

The pharmacokinetic (PK) objectives of the study:

- To assess the PK profile of ZX008 administered as a single oral dose with clobazam (CLB) + valproate (VPA) or with CLB + VPA + stiripentol (STP) in subjects ages 2-18 years of age with Dravet syndrome (Cohort 1).
- Model PK of ZX008 in single and multiple dose regimens using fenfluramine/nor-fenfluramine concentration-time data from subjects in Cohorts 1 and 2.
    - A separate analysis plan will be developed to address Cohort 1 results.

2.6 EXPLORATORY OBJECTIVES

Exploratory objectives of this study (Cohort 2) include:

- The change from baseline in health and social care resource use including planned and unplanned hospital visits, use of ambulances, general practitioner (GP) visits, speech and language therapy utilization, occupational and physical therapy utilization.
- Change from baseline in sleep quality.
- Change from baseline in meal time behavior.
- Effect of study medication on sleepiness (Karolinska Sleepiness Scale).
- Assessment of a Dravet syndrome composite endpoint including seizure frequency and severity and subjective patient-relevant outcome measures (e.g., behavior, sleepiness, etc) using data from the collected rating scales will be performed.
    - A separate analysis plan will be developed to explore this endpoint.

3. STUDY DESIGN

3.1 OVERALL STUDY DESIGN AND PLAN

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

3.2 COHORT 2 STUDY TREATMENT

The study period of cohort 2 subjects comprises a Baseline period (6 weeks), a T+M period (15 weeks: (21 days for dose titration + 12 weeks maintenance), a Taper period or transition period, and a Post Dosing visit after study completion or early termination.

Upon completion of the Baseline Period, subjects who qualify for the study will be randomized (1:1) in a double-blind manner to receive ZX008 (0.5 mg/kg/day, 20 mg/day maximum) or placebo. Randomization will be stratified by age group (<6 years, ≥6 years) to ensure balance across treatment arms, and initially it was hoped that at least 40% of subjects will be in each age group. The actual % of subjects in each stratum may be different from this goal. Subjects will be assigned a randomization number by the IVR/IWR system upon confirmation that the subject qualifies for enrollment in the Titration Period. All subjects will be titrated to their randomized dose during the Titration Period. Titration will occur in 3 steps starting with a 0.2 mg/kg/day dose of ZX008 (or placebo equivalent) on Study Days 1-7, increased to a dose of 0.4 mg/kg/day on Study Day 8-14, and then increased to a dose of 0.5 mg/kg/day on Study Days 15-21; the maximum daily dose at any point is 20 mg/day. The duration of the titration period will be 21 days.

There will be cardiac safety follow-up of 3 to 24 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. These results will be presented elsewhere.

3.2.1 Treatment Arms (Cohort 2)

The ZX008 dose of 0.5 mg/kg/day was chosen as the active dose (maximum 20 mg/day) to be used as the test arm in Cohort 2, based on the results of the cohort 1 PK study.

Treatment ARM: ZX008 – 0.5 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 0.5 mg/kg/day will be divided into twice daily doses up to a maximum of 20 mg/day.

Treatment ARM: Placebo

Placebo is identical 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.

3.2.2 Treatment Periods (Cohort 2)

Titration Period:

Study medication (ZX008 0.5 mg/kg/day or placebo) will be administered as equal doses BID in the morning and in the evening approximately 12 hours apart, with food. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may be taken later, up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given.

Administration of the IMP will be based on the subject's weight at Visit 3 (Study Day -1). At Visit 8 (Day 50), if the subject's weight has changed ±25% of the weight at Day-1, the IMP dose will be recalculated to reflect the change in weight. Subjects will be dosed using the oral dosing syringe provided.

In order to maximize tolerability, the dose for each subject will be titrated to 0.5 mg/kg/day. All subjects will start with a dose of ZX008 of 0.2 mg/kg/day (or placebo equivalent), administered in divided doses BID (maximum: 20 mg/day) on Study Days 1-7.

The dose will be increased to ZX008 0.4 mg/kg/day (or placebo equivalent) administered in divided doses BID (maximum 20 mg/day) on Study Days 8-14. The dose of ZX008 will be increased to 0.5 mg/kg/day (or placebo equivalent) administered in divided doses BID (maximum: 20 mg/day) on Study Days 15-21. The titration algorithm is shown below.

Table 2: Titration Algorithm

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

Maintenance Period:

After completion of the Titration Period, subjects will enter the Maintenance Period and continue to receive ZX008 0.5 mg/kg/day or placebo and be treated for an additional 12 weeks on stable dosage. Study medication will continue to be administered BID in the morning and in the evening, approximately 12 hours apart, with food. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given.

Taper Period:

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

The taper algorithm is indicated below.

Table 3. Taper Algorithm

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

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 (hypothetical transition is depicted in 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, or assigned dose of ZX008) to the 0.2 mg/kg dose during the 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

Randomized Dose Selected for Cohort 2	Step 1 Days 1-7 after study completion	Step 2 Days 8-14 after study completion

ZX008 0.5 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
Placebo	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
Note: maximum daily dose of ZX008 is 20 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). The transition algorithm for subjects assigned to ZX008 will depend on the final dose selected for Cohort 2. Dosage will be decreased in 0.2 mg/kg/day steps every 7 days until subjects are at a dose of 0.2 mg/kg/day.

4. SCHEDULE OF ASSESSMENTS

Table 5. Cohort 2: Schedule of Assessments

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

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

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

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

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

c: Follow-up ECG, ECHO, and physical examination will be performed 3-6 months after early termination, or for those subjects who complete the study but do not enter the open-label extension trial (see Section 6.2.6).
d: The Visit 8 ECHO must be performed any time between Study Day 40 and Study Day 54. The Visit 12 ECHO must be performed any time between Study Day 90 and Study Day 113; if a subject discontinues early from the study, the ECHO should be scheduled as soon as practical. If the Study Day 43 ECHO was completed ≤30 days prior to early termination, the Visit 12 ECHO will not be performed provided the parent/guardian agrees to bring the subject to the clinic for the cardiac follow-up visit.
e: Females of child-bearing potential
f: Plasma sample for PK assessment will be conducted prior to the dose at the Follow-up visit and 1, 2, and 4-6 hours after dose administration for Subjects continuing into the open-label extension trial.
g: Plasma sample for assessment of background AED(s) will be conducted prior to the dose of AED(s) at Visits 3, 6, 8 and 12.
h: Study drug/diary dispensed for the transition for subjects entering the open-label extension trial and for tapering for subjects exiting the study.
i: Site personnel will review study medication dosing procedure (titration) with parent/caregiver.
j: Study drug administration begins in the morning of Study Day 1.
k: Only adverse events related to cardiac safety will be collected at this visit.
l: Mandatory one time collection any time during or after screening and before Visit 10.

5. ANALYSIS POPULATIONS

5.1 COHORT 2

5.1.1 Enrolled Population

The Enrolled population includes all subjects who gave informed consent/assent.

5.1.2 Intention-to-Treat (Randomized) Population

The ITT (or Randomized) population includes all subjects randomized to receive study treatment.

5.1.3 Modified Intention-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 0.5 mg/kg/day to placebo, as well as key secondary analyses, will be performed on the mITT Population.

5.1.4 Per Protocol (PP) Population

The per protocol 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.

For cohort 2, the primary and key secondary efficacy analyses will be repeated on the PP Population.

5.1.5 Safety 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.

6. STATISTICAL METHODOLOGY

6.1 STATISTICAL AND ANALYTICAL ISSUES

6.1.1 Statistical Methods

Tabulations will be produced for demographics, baseline, efficacy, and safety parameter. 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 showing number of observations, frequencies, and percentages.

This SAP provides summary of statistical methods for comparing the regimens in the double-blind study (cohort 2).

Confidence intervals will be calculated at the 95% confidence level for key parameters or estimates as described in the sections below. Two-sided statistical significance testing (alpha level = 0.05) comparing treatment to placebo will be performed for the primary and secondary endpoints as described in the respective sections below.

All statistical analyses and summaries will be performed using SAS statistical software (Version 9.3 or later version that will be in use at the time of analysis, unless otherwise noted). Adverse events will be coded using the most recent MedDRA version available at the time of analysis and the actual version used will be footnoted in the respective adverse events summary tables. Concomitant medications will be coded using the available recent version of World Health Organization (WHO) Drug dictionary and the version used will be footnoted in the respective medications summary tables.

6.1.2 Multiplicity Strategy and Testing Hierarchy

The multiplicity issues in the statistical inference in this study arise from multiple endpoints.

The efficacy analyses will employ a serial gatekeeper strategy to maintain the Type 1 error rate at $\alpha = 0.05$ 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 one primary endpoint and two key secondary endpoints for the comparison of ZX008 0.5 mg/kg with Placebo. In order to preserve the overall Type 1 error rate at $\alpha = 0.05$, 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 ZX008 0.5 mg/kg and Placebo group. If the comparison is statistically significant at $\alpha = 0.05$ (2-sided) level, the hypothesis testing will proceed to Step 2. Otherwise formal testing of the other hypotheses stops.

Step 2: The secondary efficacy endpoint (proportion of subjects who achieve a $\geq$ 50% reduction from baseline in convulsive seizure frequency) will be compared between the ZX008 and Placebo

group. If the comparison is statistically significant at 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 longest convulsive seizure-free interval endpoint will be compared between ZX008 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

The baseline period for Cohort 2 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 a baseline assessment. Study day 1 will be the first day of study drug administration.

For the analysis of frequency of convulsive seizures endpoints where a baseline convulsive seizure frequency is needed, 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 prior to first dose from the Baseline period.

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 (Visit 12).
- Cohort 2 Subjects that complete the Treatment Period T+M starting from study Day 1 (Visit 3) through the protocol defined end of study visit (Visit 12).
- Subjects that enroll in the open label extension study.

6.1.6 Visit Windows

The following rules will be used to window data into treatment periods 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 includes time from first

	treatment start date, which includes 21 days of Titration period, 12 weeks of Maintenance period and Taper/Transition period (14 days) - 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 up to the first 21 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 the 12 week Maintenance Period. The primary efficacy endpoint is calculated based on data from the T+M period.
Taper/Transition Period	The Taper/Transition period consists of approximate 14- days 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. Patients entering the open-label extension study will first 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.

Unless specified otherwise in the relevant sections describing analyses for individual parameters, missing diary data will not be imputed for efficacy variables. Hence for subjects missing some of the daily measurements, the available data will be used. No explicit imputation will be performed for subjects who drop out prior to end of study (Visit 12).

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 dates 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.

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 dates 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 the first dose of IMP, the AE will be handled as a TEAE.
- The missing start date and end date of an AE will be imputed for the purpose of calculating treatment-emergent status and assigning events to treatment periods using the definitions given in the following table.

Adverse events

Partial /Missing Start Date	Missing day – If the AE start day is missing but month and year are present, then impute the 1st of the month unless the month and year are the same as the first dose of study drug. If this is the case, then impute the day of the first dose. Missing day and month – If the AE start day and month both are missing but year is present, then impute 1st January unless the year is the same as first dose date. If this is the case, then impute the day and month of the first dose. Completely missing – Impute the first dose date unless the end date suggests it

	could have started prior to this date, 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.
Partial /Missing End Date	Missing day – If the AE end date is missing but month and year are present, then impute the last day of the month, unless the year and month are the same as the first dose of study drug. If this is the case, then impute the date of the last dose. Missing day and month – If the AE has missing day and month but year is present, then impute 31st December. Completely Missing – Need to look at whether the AE is still ongoing before imputing a date and also when it started in relation to starting study drug. If the ongoing flag is missing, then assume that the AE is still present (i.e., do not impute a stop date). If the AE has stopped and the start date is prior to first dose date, then impute the first dose date. If the AE started on or after the first dose date, then impute an end 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 and Interaction of treatment by Site

The primary analysis will use data pooled across all investigative sites. Region (UK, US, Canada, France, Germany, Netherlands, Spain) and site differences may be explored in preliminary analyses depending on the number of subjects randomized by each site/region.

6.1.10 Determination of Sample Size

The sample size for Cohort 2 was estimated from the results of two randomized, placebo-controlled trials for the treatment of Dravet syndrome with stiripentol. The results from the two trials, STICLO France and STICLO Italy, were reported in the European Public Assessment Report (EPAR) for stiripentol (EMA, 2007). In the stiripentol groups, the standard deviation (SD) of the percentage change in seizure frequency from baseline to month 2 was 42% in the STICLO France trial and 26% in the STICLO Italy trial. The analogous SDs for placebo groups were 38% and 62%. For the current trial, an SD of 50% was assumed for the primary analysis comparing ZX008 to placebo on the change from baseline in seizure frequency. Using a two-sided test at the α=0.05 significance level, a sample size of 35 subjects per treatment group affords 90% power to detect a difference in mean change from baseline of 40 percentage points.

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 expected SD was increased to 55. Other assumptions in the sample size calculation have remained unchanged. A sample size of approximately 80 subjects (40 per arm) affords 90% power to detect a difference in mean change from baseline of 40 percentage points with 55% SD. Given the variability seen in the STICLO and Epidiolex trials, the sample size for the current trial was increased from 35 to 40 subjects per treatment arm for a total of 80 subjects.

6.2 SUBJECT CHARACTERISTICS

6.2.1 Disposition

Subject disposition will be presented per treatment group and overall.

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.

Completion and discontinuation data for all randomized subjects will be listed and sorted by treatment and site.

6.2.2 Protocol Deviations

Major protocol deviations will be summarized showing number and percent by treatment and overall based on the SAF. Major protocol deviations are those that have the potential to impact patient safety or affect data integrity. Major protocol deviations may be grouped into different important clinical 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 may be counted in more than 1 deviation category.

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

6.2.3 Demographics 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 at screening [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 genotype panel data will be descriptively summarized as per data type (categorical). Additional analyses of genetic data may be prepared in a separate report.

The primary genotype mutation for each subject will be listed for the safety population.

6.2.4 Treatment Exposure and Compliance

6.2.4.1 Treatment Exposure

Exposure will be summarized for the safety population.

Duration of exposure to treatment (i.e., time on treatment in days) will be calculated per subject as the number of days with IMP intake during the study and will be summarized using descriptive statistics (mean, standard deviation, median, and range) for the safety population. The per subject duration of exposure will be calculated as follows:

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

The duration of exposure summary statistics will be presented by treatment group for the combined Titration, Maintenance and Taper/Transition periods. Also, the exposure subject data listing will be presented.

6.2.4.2 Compliance

Compliance will be summarized for the SAF and mITT.

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 population over the course of T+M and Maintenance only, reported by treatment group.

6.2.5 Prior and Concomitant Medications and Therapies

Medications (collected on the prior/concomitant medication eCRF pages) 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 double-blind 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.

Medications will be summarized by treatment and overall for prior and concomitant medications by Anatomical Therapeutic Chemical (ATC) classification and preferred therapeutic Term (Level 2: pharmacological or therapeutic subgroup and Level 3: chemical or therapeutic or pharmacological subgroup). For each medication the number and percentage of subjects will be displayed.

Summary tables will be presented for SAF population.

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

6.2.7 Medical History

Medical history will be summarized and sorted alphabetically, by primary System Organ Class and Preferred Term coded using 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 SAF population.

6.3 EFFICACY ANALYSES

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, 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 convulsive seizure frequency (CSF) will be calculated from all available data collected during the Baseline and T+M Periods, and the treatment group MCSF 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 15 weeks (including 3 weeks titration). However, actual durations will be computed for each subject based on the individual subject's start and stop dates for each period with the exception that if the baseline period is longer than 42 days, the average for the baseline period will be the 42 days' data immediately preceding the Randomization date.

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 (CSF_{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 study period, 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 Tests

<u>T + M Period</u>:

The primary analysis will compare the ZX008 0.5 mg/kg/day group to the placebo group using a two-sided test at $\alpha = 0.05$ level of significance.

The primary endpoint (CSF_{T+M}) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group (ZX008 or Placebo) and age group (< 6 years, ≥6 years) as

classification factors, log baseline frequency (CSF_B) as a covariate in the model, and log CSF_{T+M} as response. Treatment group means and the difference from placebo will be estimated with least squares means from the analysis model along with 95% confidence intervals and associated 2-sided p-values. Estimated treatment group means and CI endpoints will be exponentiated for presentation.

The null hypothesis

$$H_0: \mu_{Z008} - \mu_P = 0,$$

will be tested against the alternative

$$H_A: \mu_{Z008} - \mu_P \neq 0,$$

where μ_{Z008} and μ_P represent the ZX008 0.5 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 bigger reduction in mean convulsive seizure frequency from baseline 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 ZX008 0.5 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 indicating placebo, and 0.5 mg groups).

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

Additional statements may be used to obtain estimates and 95% confidence interval. 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. If normality assumptions are not met, the results of the nonparametric test will be used to assess the primary objective.

Treatment by Baseline Seizure Category:
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

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.

6.3.1.2 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 and 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 as the response variable, baseline CSF as a covariate, and treatment and age stratum as classification factors. A parametric ANCOVA will then be used to compare ZX008 treatment group to placebo treatment group.

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

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 for the mITT population. It is conceivable that some or all of the supplemental analyses may not reach statistical significance. However, it is expected that the direction of effect will be consistent in favor of ZX008 versus Placebo.

6.3.2 Key Secondary Analyses

6.3.2.1 Proportion of subjects with ≥50% Reduction from Baseline in Convulsive Seizure Frequency (50% Responder Rate)

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 0.5 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.

The comparison between ZX800 treatment group and Placebo group 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 at least a 50 percentage point reduction, yes or no) as a function of treatment (ZX008 and placebo), baseline seizure frequency and age group (< 6 years, ≥6 years).

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 0.5 mg/kg/day to placebo.

6.3.2.2 Proportion of subjects with 0 or 1 Convulsive Seizures

The proportion of subjects with either 0 or 1 convulsive seizure will be identified, descriptive statistics will be presented by treatment group, and will include the number and proportion of subjects.

A Fisher's exact test will compare the proportion of subjects with a 100% reduction, and also with at most 1 convulsive seizure, in the ZX008 0.5 mg/kg/day to the analogous proportion in the placebo group.

6.3.2.3 Longest Convulsive Seizure-Free Interval

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 end of the current seizure-free interval will be 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 ZX800 and placebo, and the p-value from this test will be presented. Boxplots of the longest interval data will accompany all descriptive statistics and all data will be provided in a data listing.

6.3.3 Additional Secondary Endpoint Analyses

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)

The ZX008 treatment group will be compared to the placebo on the number of seizure free days per 28 days during T + M using a similar approach as the primary analysis incorporating the baseline seizure-free frequency as a covariate.

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

A step-function 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 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 using the same method employed for the ≥50% reduction from baseline endpoint.

6.3.3.3 Change from Baseline in Non-Convulsive Seizure Frequency

Algorithms for calculating mean non-convulsive seizure frequency and change from baseline will follow the same methods as described for the primary endpoint.

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

The statistical comparison of treatment group and placebo will be done using a nonparametric ANCOVA similar to the method described in 6.3.1.1. Here the analysis will use the ranks of the non-convulsive seizure frequencies as the response variable, treatment as a factor, and the ranks of the baseline non-convulsive seizure frequencies as a covariate. Data will be displayed by treatment group as described for the primary endpoint.

6.3.3.4 Change from Baseline in Convulsive Seizure Frequency by Seizure Type

Algorithms for calculating mean convulsive seizure frequency and change from baseline for each seizure type (GTC, tonic, clonic, hemiclonic, tonic-atonic, and focal seizures with an observable motor component) will follow the same methods as described for the primary endpoint.

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

The statistical comparison of treatment group and placebo will be done using a nonparametric ANCOVA similar to the method described in 6.3.1.1. Here the analysis will use the ranks of the non-convulsive seizure frequencies as the response variable, treatment as a factor, and the ranks of the baseline non-convulsive seizure frequencies as a covariate. Data will be displayed by treatment group as described for the primary endpoint.

6.3.3.5 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.

The statistical comparison of treatment group and placebo will be performed using a nonparametric ANCOVA similar to that described above for the analysis of non-convulsive seizures. Data will be displayed by treatment group as described for the primary endpoint.

6.3.3.6 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. The second and third round might use medications or doses different from 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 for the T + M period by the mean, standard deviation (SD), median and range. The ZX008 treatment group will be compared to the placebo group using a rank ANCOVA analogous to that described in Section 6.3.1.1. Specifically, the ANCOVA will use ranks of rescue medication frequency during T+M as the response, and will incorporate treatment group as a classification factor and the ranks of rescue medication frequency during Baseline as a covariate.

6.3.3.7 Hospitalization and Other Resource Utilization to Treat Seizures

In order to better understand the healthcare resource burden associated with the management of Dravet syndrome, caregivers will be asked which of the following hospital and community-based healthcare services they had interactions with over the preceding month: emergency room services, ambulance, planned and unplanned hospitalization, family physician services, speech

and language therapy, occupational therapy, and physical therapy. This information will be captured in the CRF.

6.3.3.8 Incidence of Status Epilepticus

The incidence of status epilepticus will be evaluated based on cases captured as such with emergency treatment at treatment centers and entered as adverse events into the safety database, and also as convulsive seizures lasting longer than 10 min from the seizure diary. According to the International League Against Epilepsy definition, seizures over five minutes 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, 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.

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 related to hospitalization for SE and seizures entered into the diary as seizures > 10 min. (The definition of SE includes seizures lasting 5 min or longer, so not all SE will be recorded in the >10 min category.)

To ensure that all instances of SE are accounted for, a composite endpoint will be constructed that combines episodes of SE recorded as AEs with any other convulsive seizure with a duration > 10 min. The ZX008 and placebo groups will be compared on the composite endpoint using a Cochran-Mantel-Haenszel test with age group as stratification factor.

6.3.3.9 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.

6.3.3.10 Quality of Life in Childhood Epilepsy (QOLCE) Scale

The parent/caregiver will complete this questionnaire for this assessment that looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, well-being, cognition, social activities, behavior and general health, at baseline period (Visit 3), at Maintenance period (Visit 8) and at End of study (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, a score for each subject for each subscale is calculated by averaging that subject's responses to each item in the subscale. 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 is then calculated for each subscale including the overall quality of life. The higher the subscale and overall quality of life scores, the better the response.

Table 2: Subscales 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, and 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	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 the above 16 subscale scores

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 each QOLCE subscale score will be calculated for each subject by subtracting the baseline score from the 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 a Wilcoxon test.

Individual subject data for the domains will be listed.

6.3.3.11 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 a Wilcoxon test.

The next two ratings evaluate the change from baseline in the responsible parent/caregiver's quality of life during the time the subject is in the trial:

6.3.3.12 Change from Baseline in the 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 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 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 time point.

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 a Wilcoxon test.

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

6.3.3.13 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. The change from baseline will be calculated and ZX008 and placebo groups will be compared using the same methods as specified for the PedsQL 4.0 analysis.

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

The parent/caregiver will rate their global impression of the subject's condition during Titration period (Visit 5 and 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 time point. 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-I data will be listed.

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

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

6.3.4 Exploratory Analyses

6.3.4.1 Change from baseline in sleep quality

The parent/caregiver will be asked to indicate the appropriate response that adequately describes their child's sleep quality since starting IMP at Titration period (Visit 6), Maintenance period (Visit 8 and 10), and at End of study (Visit 12). The following question will be asked:

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

The response will be noted as below-

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

For each time point, the number and % of subjects in the response categories will be presented, by treatment group.

All sleep quality assessment data will be presented in the subject data listing.

6.3.4.2 Change from baseline in meal time behavior

The parent/caregiver will be asked to indicate the appropriate response that adequately describes their child's eating behavior since starting IMP at Titration period (Visit 6), Maintenance period (Visit 8 and 10), and at End of study (Visit 12). The following question will be asked:

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

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

For each time point, the number and % of subjects in the response categories will be presented, by treatment group.

6.3.4.3 Change from baseline on Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale will be administered according to the schedule visit time points in Table 1. The Karolinska Sleepiness scale is a self-report scale that measures the subject's drowsiness. It is a 9-point verbally anchored scale, which ranges from 'extremely alert' at one end of the scale to 'extremely sleepy – fighting sleep' at the other end of the scale. Within this study, the scale will be completed by the observer in an exploratory manner.

Score	Description
1	Extremely alert
2	Very alert
3	Alert
4	Rather alert
5	Neither alert nor sleepy
6	Some signs of sleepiness
7	Sleepy, but no effort to keep awake
8	Sleepy, some effort to keep awake

9	Very sleepy, great effort to keep awake, fighting sleep

Descriptive statistics will be presented for each time point where measured and will include number and percent of subjects in each category, mean, standard deviation, median, minimum and maximum. The ZX008 0.5 mg/kg/day and placebo groups will be compared on change from baseline using a Wilcoxon rank sum test.

Additionally, scores of 1-6 will be categorized as "Active" and scores of 7-9 categorized as "Sleepy". These categorizations will be summarized using counts and percent (%) of subjects by treatment by each visit time point. A Fisher's exact test will compare the proportion of subjects reporting sleepy scores (7, 8 or 9) in the ZX008 0.5 mg/kg/day to the analogous proportion in the placebo group.

All Karolinska Sleepiness data will be presented in the subject data listing.

6.3.4.4 Assessment of a Dravet Syndrome Composite Endpoint

As stated in the protocol, a Dravet syndrome composite endpoint will be created using outcome measures from the protocol to create a composite endpoint to assess treatment of Dravet syndrome without emphasis on a single endpoint. The outcomes under evaluation in this study will include measures for example such as seizure frequency, behaviour, quality of sleep, and others. The measures to select the composite are identified as part of a project with physician interviews and interviews with patient's families and are part of a project on multi-dimensional outcome measures discussed in the protocol. A separate SAP will be developed to describe the exploratory analyses that test the psychometric development and performance (or measurement accuracy) of the core outcome measures for the composite endpoint and the results will be reported separately.

6.4 SAFETY ANALYSES

All safety analyses will be performed for the Safety population (SAF) and will be reported by treatment group, and overall.

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. All other AEs occurring after enrollment and prior to the first administration of study treatment are defined as non-treatment emergent AEs (non-TEAEs).

Any missing relationship will be considered as "related."

The severity of AEs (whether non-serious 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.

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 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.
- TEAE leading to treatment discontinuation
- 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 adverse events by system organ class (SOC) and preferred term (sorted alphabetically) for each treatment group and overall:

- All TEAEs

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

An additional summary 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.

The summaries will be provided for the double-blind treatment period. 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.

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 14 of protocol)-

Table 5 – Adverse Events of Special Interest:

Metabolic/Endocrine
1. Elevated prolactin level ≥2x above the upper limit of normal (ULN)
Neuropsychiatric
1. Suicidal thoughts, ideation or gestures

All adverse events of special interest will be 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, end of study (EOS) visit, and at the Cardiac follow-up visit for patients who do not enter the open-label extension study. An abbreviated physical exam is performed at Day 15 (Visit 5), 22 (Visit 6), 50 (Visit 8), 78 (Visit 10) and at the Cardiac follow-up visit for patients who do not enter the open-label extension study.

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

6.4.4 Neurological Examination

A complete neurological examination will be performed at Screening Visit (Visit 1) and EOS (Visit 12).

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 5 and visit 6), and maintenance period (visit 8 and visit 10) and at EOS visit (visit 12).

The mean values and change from baseline to each on-study visit time point 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. The most extreme abnormal values for each subject will also be listed.

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 50 (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.

6.4.7 Doppler Echocardiography

Doppler echocardiography 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 table below:

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

or pulmonary) • Mean Mitral valve gradient ≥ 4 mmHg • Mean Aortic valve gradient ≥ 15 mmHg • Mean Tricuspid valve gradient > 4mmHg • Mean Pulmonary valve gradient > 21mmHg	• Mean Aortic valve gradient < 15 mmHg • Mean Tricuspid valve gradient < 4mmHg • Mean 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:

>7 years to <=11,

>11 years to <=15,

>15 years 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 2.

The following laboratory parameters will be summarized:

- Hematology: hemoglobin, hematocrit, erythrocytes, erythrocyte mean corpuscular volume, leukocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets
- Blood Biochemistry: albumin (ALB), alkaline phosphatase (AP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bicarbonate, blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2), chloride (Cl), creatinine, creatine kinase, gamma-glutamyl transferase (GGT), globulin, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), thyroid function (T3, T4, and thyroid stimulating hormone [TSH]), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid.
- Tests of growth and precocious puberty: Growth hormone (GH), insulin-like growth factor-1 (IGF-1, low sensitivity), prolactin, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), testosterone, estradiol
- Coagulation: Prothrombin time (PT)/International normalized ratio (INR), activated partial thromboplastin time (PTT)
- Whole blood cannabidiol (CBD)
- Urinalysis: analysis for pH, glucose, ketones, nitrite, protein, bilirubin, urobilinogen, leukocyte esterase, and occult blood. Microscopic analysis will be performed for blood, all cell types, and casts.
- Urine pregnancy test: Urine pregnancy testing will be performed in female subjects of childbearing potential.
- Urine THC panel

Observed continuous laboratory data will be 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 in each category 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 Clinical Significant laboratory results will be provided. In this listing, those values outside the sponsor defined alert ranges will be marked and further available details about clinical relevance and diagnosis will be added.

A special listing will be presented which will provide for each subject and each lab parameter the maximum out-of-range value over both Baseline and during the T+M period. The visit on which this highest or lowest value occurred will be included.

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 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.

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)

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). The change from baseline in the ZX008 and placebo groups will be compared using Wilcoxon tests.

6.5 PHARMACOKINETICS (PK/PD) ANALYSIS

The results of the analysis of PK data collected in subjects from Cohort 2 will be reported separately.

In the main report (CSR), individual subject plasma concentration data from cohort 2 will be listed. Summary statistics for the concentration data will be provided by analyte.

6.6 ANALYSIS OF OTHER ASSESSMENTS

Not applicable.

6.7 INTERIM ANALYSIS

No formal interim analysis of this specific study is planned.

6.8 INDEPENDENT DATA AND SAFETY MONITORING COMMITTEE

The IDSMC is an independent advisory body that monitors participant safety, data quality and progress of the clinical trial. The IDSMC charter will outline the roles and responsibilities of the committee and guide its operations and frequency of meetings. The IDSMC will consist of individuals external to the sponsor who have relevant clinical trial expertise and experience in safety assessment.

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

The 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

- Protocol states that safety data will be summarized separately for the titration and maintenance periods as well as for the combined T+M period. Instead safety will be summarized only for the combined T+M..
- Protocol states that subjects in the safety population will be summarized by the treatment actually received. However, safety data will be presented by randomized treatment group except where noted otherwise.
- Protocol states 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.

- The protocol stated that the longest interval between convulsive seizures will be analyzed using a log-rank test. Instead groups will be compared with a Wilcoxon test.
- Responder analyses – The protocol included a ≥40% response analysis as one of the key secondary endpoints. It was decided to not include this in the hierarchical testing of secondary endpoints.
- An analysis of the percentage of subjects who achieve a 25% reduction in seizures was added.,
- 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 further states that the cognition subscale of the BRIEF will be used to evaluate cognition. The BRIEF and the BRIEF-P will be used to evaluate cognition.
- The Protocol states the Clinical Global Impression ratings by Investigator and Caregiver are exploratory endpoints. They are secondary endpoints.
- The protocol states the sample size is approximately 70 randomized subjects. As explained in Section 6.1.10, the sample size was adjusted to approximately 80 randomized subjects based on data from the completed study of Epidiolex in Dravet syndrome.

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8. APPENDICES

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