16.1.9 Documentation of Statistical Methods

The document listed below is provided in this section.

Statistical Analysis Plan (Study ZX008-1601 Part 2) dated 12-October-2022

Statistical Analysis Plan for Cardiovascular Endpoints (Study ZX008-1601 Part 2) dated 22-February-2023

Statistical Analysis Plan for Interventional Studies

Study ZX008-1601 Part 2 Statistical Analysis Plan

Sponsor Name: Zogenix International Limited, an indirectly wholly owned subsidiary of Zogenix Inc. which is a directly wholly owned subsidiary of UCB Biosciences
Protocol Number: ZX008-1601
Protocol Title: A Two-Part Study of ZX008 in Children and Adults with Lennox-Gastaut Syndrome (LGS); Part 1: A Randomized, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults with LGS, Followed by Part 2: An Open-label Extension to Assess Long-Term Safety of ZX008 in Children and Adults with LGS

Protocol Version and Date: (DD-Mmm-YYYY):
13-Jan-2017 Version 1.1
10-Jan-2018 (Amendment 1 Rest of World)
20-Jun-2019 (Amendment 2.0)
29 July 2019 (Amendment 2.1)
02-Jul-2020 (Amendment 3.1)
29-Jul-2020 (Amendment 3.2_Japan)
25-Jul-2022 (Amendment 4.0_Japan)

Syneos Health Project Code: 1009529A

Authors: [redacted] Principal Biostatistician

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Revision History

Version #	Date (DD-Mmm-YYYY)		Revision Summary
0.1	04-Jun-2020	[redacted]	Initial Release Version
0.2	22-Jun-2020		Modifications per request
0.3	30-Jun-2020		Modifications per request
1.0	07-Jul-2020		Finalization
2.0	16-Oct-2020		Modifications for Interim Analysis
2.1	07-Jan-2021		Finalization for Interim Analysis
3.0	22-Jan-2021		Finalization for Interim Analysis – new Status Epilepticus Event summaries.
3.0	25-Jan-2021		Finalization for Interim Analysis
3.0	27-Jan-2021		Last Revisions for Interim Signoff
4.0	27-May-2021		Addition of --new PRE-DCR outputs to Table of contents --All Countable Seizures that did not result in drops parameter tables --TEAEs by maximum severity --Weight summary by age --Sensitivity to cluster imputation --Sensitivity to SE analyses --added CGI and additional exploratory analyses to the Interim Analysis plans
4.0	16-Jun-2021		Signoff
5.0	12-Oct-2022		Updates for Japanese PCA

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

Approvals

Syneos Health Approval

[redacted] Principal Biostatistician	[redacted]	*Electronically signed by: [redacted]* *Reason: I am the author* *Date: Nov 15, 2022 10:23 EST*
Name, Title	Signature	Date (DD-Mmm-YYYY)

[redacted] Principal Biostatistician	[redacted]	*Electronically signed by: [redacted]* *Reason: I am the reviewer* *Date: Nov 15, 2022 11:02 EST*
Name, Title	Signature	Date (DD-Mmm-YYYY)

Zogenix International Limited Approval

[redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 09-Nov-2022 | 12:10 PST 887BA57009644951985D71FB157FD07B	09-Nov-2022 | 12:10 PST
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[redacted] Statistician on behalf of Zogenix International Limited	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 09-Nov-2022 | 22:48 PST 3AC910E51AB3403D9ACEE0F94527504B	09-Nov-2022 | 22:49 PST
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Table of Contents

1 Glossary of Abbreviations

Abbreviation	Description
AE	adverse events
AED	Antiepileptic Drugs
AESI	adverse event of special interest
ALB	albumin
ALT;SGPT	alanine aminotransferase
AP	alkaline phosphatase
AS	atonic seizures
AST; SGOT	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice a day
BMI	body mass index
BRI	Behavioral Regulation Index
BRIEF	Behavior Rating Inventory of Executive Function
BUN	blood urea nitrogen
Ca	calcium
CBD	cannabidiol
CDC	Center for Disease Control
CGI-I	Clinical Global Impression – Improvement
CI	confidence interval
CL	chloride
CMH	Cochran-Mantel-Haenszel
CO2	carbon dioxide
CS	clonic seizures
C-SSRS	Columbia-Suicide Severity Rating Scale
DCR	Data Change Request
DSD	Daily Seizure Diary
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic Case Report Form
EMI	Emergent Metacognition Index
ESC	Epilepsy Study Consortium
ET	Early Termination
FI	Flexibility Index
FS	focal seizures
FSH	Follicle Stimulating Hormone
GEC	Global Executive Composite
GGT	gamma-glutamyl transferase
GH	Growth hormone

Abbreviation	Description
GTC	generalized tonic-clonic seizures
HADS	Hospital Anxiety and Depression Scale
HS	hemiclonic seizures
ICH	International Conference on Harmonisation
IGF-1	insulin-like growth factor-1
IMP	Investigational Medicinal Product
INR	International normalized ratio
ISCI	Inhibitory Self-Control Index
IWR	Interactive Web Response system
K	potassium
kg	kilogram
LDH	lactate dehydrogenase
LGS	Lennox-Gastaut syndrome
LH	Luteinizing Hormone
M	Maintenance Period
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	Metacognition Index
mITT	Modified Intent-to-Treat
MS	myoclonic seizures
MS	myoclonic seizures
Na	sodium
OLE	Open Label Extension
PBPK	physiologically-based pharmacokinetic
PCA	Partial Change Application
PK	pharmacokinetics
PT	Preferred Term
PT	Prothrombin time (PT)
PTT	partial thromboplastin time
Q_1	25th Percentile / 1st Quartile
Q_3	75th Percentile / 3rd Quartile
QoL	Quality of Life
QOLCE	Quality of Life in Childhood Epilepsy
SAF	Safety Population
SAP	statistical analysis plan
SD	standard deviation
SE	status epilepticus
sNDA	Supplemental New Drug Application
SOC	System Organ Class

Abbreviation	Description
SOP	Standard Operating Procedures
STC	secondarily tonic-clonic
STP	stiripentol
T+M	Titration and Maintenance Periods
TA	tonic/atonic seizures
TEAE	Treatment-emergent adverse events
THC	Tetrahydrocannabinol
TLF	tables, data listings, figures
TS	tonic seizures
TSH	thyroid stimulating hormone
USA	United States of America
VABS	Vineland Adaptive Behavior Scale
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

2 Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the summary tables, figures, and data listings that will be produced for Part 2 of the trial, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. The analyses for Part 1 are detailed in a separate SAP.

2.1 Responsibilities

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

Separate analysis plans for ECG/ECHO will be produced.

Clario will provide analyses of ECG and ECHO data.

2.2 Timings of Analyses

Study 1601 is an international multicenter study being conducted in two parts. Up to approximately 80 study sites in North America, Europe, Australia, and Japan are planned to participate. Part 1 is a double-blind, parallel-group, placebo-controlled, study to assess the efficacy and safety of two doses of ZX008 when used as adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children and adult subjects. Part 2 is an open-label, long term (1 year for Cohort A; up to 6 years for Cohort B) extension study.

Study 1601 includes 2 cohorts: Cohort A includes subjects from North America, Europe, and Australia; Cohort B includes subjects from Japan. Analyses from Part 1, Cohort A are completed. Cohort B will be analyzed after all subjects have reached specified time points in the study or have discontinued from the study. Multiple analyses of Cohort B may be completed.

All objectives will be evaluated in Cohort A and B independently. Data from Part 2, Cohort A will be analyzed with an interim analysis when all Cohort A subjects have completed 1 year in Part 2 and a final analysis after all Cohort A subjects have completed Part 2 or have transitioned to another study. Data from Part 2, Cohort B will be analyzed independently with an interim analysis after the last subject in Cohort B completes 12 months in Part 2 and a final analysis when the last subject in Cohort B completes Part 2 or exits the trial.

Analysis results for Part 2 from Cohort A and B may be compared through descriptive statistics and if reasonable, some analyses may be performed using data from Cohorts A and B combined.

3 Part 2 Study Objectives

3.1 Primary Objective for Part 2

The primary objective of Part 2 is to assess the long-term safety and tolerability of ZX008 in children and adults with LGS with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, Tanner Staging, cognition (BRIEF), vital signs (blood pressure, heart rate, temperature, and respiratory rate), ECG, ECHO, body weight, and body mass index (BMI).

3.2 Secondary Objective(s)

The secondary objectives of Part 2 are:

To assess treatment with ZX008 relative to the pre-ZX008 baseline on the following effectiveness measures:

- The change in the frequency of seizures that result in drops
  - Seizures that result in drops include seizures of the following types that have been reviewed and confirmed for each subject as a drop seizure by the Epilepsy Study Consortium (ESC): generalized tonic-clonic seizures [GTC], secondarily generalized tonic-clonic seizures [SGTC], tonic seizures [TS], atonic seizures [AS], tonic/atonic seizures [TA].
- The change in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) between baseline and the Open Label Extension (OLE) Treatment Period whether ESC confirmed as drop or not.
- The change in the frequency of all countable motor seizures (GTC, SGTC, TS, AS, TA, clonic seizures [CS], focal seizures with clear observable motor signs [FS], and hemiclonic seizures [HS])
- The change in the frequency of all countable non-motor seizures (absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms)
- The change in the frequency of all countable (i.e., motor and non-motor) seizures (GTC, SGTC, TS, AS, TA, absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms)
- The proportion of subjects who have a worsening or no change (i.e., $\leq$ 0% reduction), >0 %, $\geq$ 25%, $\geq$ 50%, $\geq$ 75%, 100% reduction, and “near seizure freedom” (i.e., 0 or 1 seizures) in frequency of all seizures that result in drops (ESC confirmed), typical drop seizures, all countable motor seizures, all countable non-motor seizures, and all countable seizures
- Number of seizure-free days, defined as 1) days with no seizures that results in drops (ESC confirmed), and 2) days with no countable motor seizures
- Longest interval between seizures that result in drops (ESC confirmed)

To evaluate the effect of ZX008 on the following endpoints:

- Clinical Global Impression – Improvement rating, as assessed by the Principal Investigator.
- Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver.

3.3 Exploratory Objectives for Part 2

The exploratory objectives of Part 2 are:

- To determine the incidence of the following on subjects receiving ZX008:
  - The incidence medical services used to treat seizures
  - The incidence of status epilepticus
  - The use of rescue medication
- To assess the effect of ZX008 on the following measures:
  - The change from baseline in affective symptoms of the parent/caregiver using the Hospital Anxiety and Depression Scale (HADS)
  - The change from baseline in quality of life (QoL) using the Quality of Life Childhood Epilepsy (QOLCE)
  - The change from baseline in caregiver burden using the Zarit Caregiver Burden Inventory

3.4 Brief Description

Study 1601 is an international multicenter study being conducted in two parts. Up to approximately 80 study sites in North America, Europe, Australia, and Japan are planned to participate. Part 1 is a double-blind, parallel-group, placebo-controlled, study to assess the efficacy and safety of two doses of ZX008 when used as adjunctive therapy for seizures in children and adult subjects with LGS. Part 1 will include 2 cohorts: Cohort A will include randomized subjects from North America, Europe, and Australia; Cohort B will include randomized subjects from Japan. The main analyses for the study, including the primary and key secondary study endpoints are assessed from Part 1, Cohort A data. Part 2 will be an open-label, flexible-dose extension for subjects completing Part 1 of the study. Data from Part 2, Cohort A will be analyzed with an interim analysis after at least 90% of Cohort A subjects have either withdrawn or completed 1 year in Part 2 and a final analysis after all Cohort A subjects have completed Part 2 or have transitioned to another study. Data from Part 2, Cohort B will be analyzed independently with an interim analysis after the last subject in Cohort B completes 12 months in Part 2 and a final analysis when the last subject in Cohort B completes Part 2 or exits the study.

Part 1 consists of a 4-week baseline, 2-week titration, 12-week maintenance, and 2-week taper or transition period. The 4-week Baseline Period includes establishment of initial eligibility during a screening visit to include an assessment of cardiac parameters (ECG and ECHO), followed by an observation period where subjects will be assessed for baseline seizure frequency based on recordings of daily seizure activity entered into a diary. Upon completion of the Baseline Period, subjects who qualify for the study are randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 mg/day [or 0.5 mg/kg/day, maximum 20 mg/day, for subjects taking concomitant stiripentol [STP]) or placebo. Randomization is stratified by weight (< 37.5 kg, ≥ 37.5 kg) to ensure balance across treatment arms, and at least 25% of subjects will be in each weight group. All subjects are titrated to their blinded randomized dose over a 2-week Titration Period. Following titration, subjects continue treatment at their randomly assigned dose over a 12-week

Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is 14 weeks. Subjects will have ECG and ECHO assessments at weeks 6 and 14 during the Maintenance Period. At the end of the Maintenance Period (or early discontinuation), all subjects undergo a blinded 2-week taper or transition period (Post-Dosing Follow-Up) depending on whether they exit the study or are enrolled in Part 2, the long-term open-label extension, respectively. Cardiac safety follow-up visits are performed after study drug discontinuation for early termination, or for those subjects who complete the study but do not enter the open-label extension part. All subjects are required to have follow-up visits at 3 and 6 months if there are any findings at a post-dose follow-up, a follow-up visit will be scheduled every 3 months until resolved or stabilized.

Part 2 is an open-label, long-term safety study of ZX008 for subjects who have successfully completed 14 weeks of treatment (Titration + Maintenance) in Part 1 and are candidates for continuous treatment for an extended period of time; subjects who have not completed the entire 14 weeks of treatment in Part 1 may be eligible to participate in Part 2 on a case-by-case basis and only following sponsor approval. Part 2 consists of a 12-month Open-Label Extension (OLE) for Cohort A and up to 72 months for Cohort B. Treatment Period and a 2-week Post-Dosing Period. Thus, subjects who were randomized to ZX008 during Part 1 and complete Part 2 will have been treated with ZX0008 for at least 70 weeks (including their participation in both Part 1 and Part 2).

During Part 2 all subjects are treated initially with 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study subjects. After 1 month at a dose of 0.2 mg/kg/day, the investigator may adjust the dose for each subject based on effectiveness and tolerability. Dose changes should be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day (or 0.5 mg/kg/day for subjects taking concomitant STP) but not to exceed total dose of 30 mg/day (or 20mg/kg/day for subjects taking concomitant STP). During the 12-month OLE subjects will have ECG and ECHO assessments at months 1, 3, 6, and 9, and at the end of study visit, and Cohort B subjects will have the additional assessments every three months from months 15 through 69.

Additionally, during at least the first 6 months of the Part 2 OLE Treatment period, subjects will continue to receive their existing antiepileptic drugs (AEDs) at the same dose and frequency as prior to starting Part 2. However, once the subject has been stable on a ZX008 dose for at least 6 months with good seizure control, Investigators will be allowed as per typical clinical practice to alter one or more other concomitant AED doses as deemed clinically appropriate. Subjects who achieve robust seizure control may be considered to decrease concomitant AEDs earlier than 6 months after review/ discussion with the Medical Monitor and approval from the Sponsor. Concomitant AEDs may be withdrawn completely but all subjects must remain on a minimum of 1 concomitant AED plus ZX008.

A follow-up ECG and ECHO will be performed at 3 and 6 months after discontinuation of ZX008 for early termination and for those subjects who complete Part 2 and do not continue with ZX008 (or fenfluramine or Fintepla) treatment (i.e., in another trial or using commercial product). Follow-up ECG and ECHO data will not be presented as part of the data analysis described in this SAP. Subjects enrolled

in Germany, France, and Netherlands will have an additional follow-up at 24 months after discontinuation of ZX008. If there are any findings at a post-dose follow-up, another follow-up will be scheduled every 3 months until resolved or stabilized. In both Part 1 and Part 2 parents/caregivers will use a diary every day to record the number of seizures, type of seizures, time and duration of seizures, whether the seizure resulted in a drop, dosing of study drug, and use of rescue medication.

3.5 Subject Selection

Subjects who participate in Part 2 must meet the full inclusion and none of the exclusion criteria for Part 2 as stated in Protocol Section 4.3.

3.6 Determination of Sample Size

The sample size of Part 2 will be determined by the number of subjects in Part 1 who are eligible for and meet the necessary criteria for Part 2. The assumptions for the sample size in Part 1 are provided in the Part 1 SAP.

3.7 Treatment Assignment & Blinding

The description of the treatment assignment for Part 1 is provided in the Part 1 SAP. Part 2 of the study is open-label.

3.8 Administration of Study Medication

Dosing in Part 2 is flexible, up to 0.8 mg/kg/day divided into two daily doses (maximum of 30 mg/day; subjects taking concomitant STP will receive up to 0.5 mg/kg/day, up to a maximum of 20 mg/day). ZX008 drug product is provided in a concentration of 2.5 mg/mL in 1 bottle size with nominal fill volume of 120 mL.

During the Part 2 OLE Treatment period, all subjects will be treated initially with 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study subjects. After 1 month at a dose of ZX008 0.2 mg/kg/day, the Investigator may adjust the dose of each subject based on effectiveness and tolerability.

Administration of the initial IMP will be based on the 0.2 mg/kg/day (maximum 30 mg/day or 20 mg/day for subjects taking concomitant STP) dose and subject's weight at Visit 15 (Part 2; Study Day 1). At Visits 19, 20, and 21 of Part 2 (Months 3, 6, and 9), if the subject's weight has changed ± 25% of the weight from Visit 15, the IMP dose will be recalculated. Subjects will be dosed using the oral dosing syringe provided.

Dose increases should not occur earlier than every 14 days at each dose level. Dose increases may only occur after a review of the diary and reported AEs, and if, in the Investigator's opinion, seizure frequency, severity, and/or duration indicates a change in medication regimen is warranted. Temporary dose decreases for tolerability can occur at the Investigator's discretion, in dose amounts and frequency appropriate for the situation. Subsequent dose rechallenge should occur at the Investigator's discretion in consultation with the Medical Monitor. ZX008 dose adjustments outside of these parameters should be discussed with the Medical Monitor and must be approved by the Sponsor prior to initiation.

Study medication will be administered as equal doses twice a day (BID) in the morning and in the evening, approximately 12 hours apart. 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. If the parent/caregiver is unable to administer the full dose due to spillage (e.g., dose was spilled during measuring, subject spit dose out during administration), he/she should attempt to give the full dose noting the extra amount used to fulfill the dose. If the subject vomits within the first 15 minutes of administration the dose may be readministered. Care must be taken not to overdose. If the amount spilled is not known, the parent/caregiver should not give additional medication to avoid potential overdose.

Full details on study drug administration, including provisions for dose adjustments, are described in the Protocol.

All subjects who complete the Part 2 OLE Treatment period and do not continue to receive ZX008 in another extension study, and those who discontinue from the study early will be tapered off of study medication. The tapering scheme is a 2-step process as described in Table 1.

Table 1:Taper Algorithm for Part 2

Current Dose	Taper Step 1 Days 1-4 after study completion or early termination	Taper Step 2 Days 5-8 after study completion or early termination
ZX008 0.2 mg/kg/day	Not applicable	Not applicable
ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day	Not applicable
ZX008 0.5 mg/kg/day (for subjects taking concomitant STP)	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.6 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day

3.9 Study Procedures and Flowchart

The full list and timing of study procedures is provided in Table 2.

Table 2: Schedule of Study Procedures

Study Assessments – PART 2		**OLE Treatment Period****						**Post-Dosing**	**Cardiac Follow-up**
Visit Number	**Visit 15[a]**	**Visit 16[b]**		**Visits 17-21 (Months 1, 2, 3, 6 and 9**)**	**Visit 22[C] (EOS/ET Cohort A) / Visit 22 (Month 12 Cohort B)**	**Visits 23-29 [Cohort B only] Months 15, 18, 21, 24, 27, 30, 33**	**Visit 30 (EOS/ET Cohort B)**	**Visit 23 (Cohort A)/ Visit 31 (Cohort B)**	**Visit 24 and 25 (Cohort A)/ Visit 32 and 33 (Cohort B)**
OLE Study Day	**1[a]**	**15**		**30, 60, 90, 180, and 270**	**365**	**450, 540, 630, 720, 810, 900, 990**	**1080 (Cohort B)**	**379[k,q] (Cohort A) 1094 (Cohort B)**	**(3-24 months post last dose)[d, k]**
		Clinic	**Phone**						
Informed Consent	X				X**	X			
Entry Criteria	X								
Demographics	X[a]								
Medical/Neurological History	X[a]								
Epilepsy History	X[a]								
Physical Examination, complete	X[a]				X		X		X
Physical Examination, abbreviated		X[m]		X[m]		X[m]		X[m]	X
Neurological Examination, complete	X[e]				X		X		
Neurological Examination, abbreviated		X[m]		X[m]		X[m]		X[m]	
Vital signs	X	X		X	X	X	X		
Weight	X[a]	X		X	X	X	X	X	
Height	X[a]				X		X		
12-lead ECG	X[a]			X	X	X[s]	X[s]		X
Doppler ECHO	X[a]			X[f,g]	X	X[g]	X		X
EEG (Italy only)	X			X[p]	X		X		
Chest x-ray (France, Netherlands only)					X		X		X

Study Assessments – PART 2		**OLE Treatment Period****						**Post-Dosing**	**Cardiac Follow-up**
Visit Number	**Visit 15[a]**	**Visit 16[b]**		**Visits 17-21 (Months 1, 2, 3, 6 and 9**)**	**Visit 22[C] (EOS/ET Cohort A) / Visit 22 (Month 12 Cohort B)**	**Visits 23-29 [Cohort B only] Months 15, 18, 21, 24, 27, 30, 33**	**Visit 30 (EOS/ET Cohort B)**	**Visit 23 (Cohort A)/ Visit 31 (Cohort B)**	**Visit 24 and 25 (Cohort A)/ Visit 32 and 33 (Cohort B)**
Urine or Serum Pregnancy Test[h]	X[a]			X[n]	X	X	X		
Clinical laboratory evaluation (hematology/chemistry/urinalysis[r], etc.)	X[i]	X[i]		X[n]	X	X[s]	X[s]		
Whole blood CBD/ THC Panel	X[a]			X[n]	X		X[s]		
Plasma sample for background AEDs		X[m]		X[n]	X	X[s]	X[s]		
Tanner Staging (for subjects >7 to 18 years old)	X[a]			X[j]	X		X[s]		
C-SSRS	X[a]			X	X	X	X		
CGI-I (assessed by parent/caregiver)	X[a]			X	X	X	X		
CGI-I (assessed by Principal Investigator)	X[a]			X	X	X	X		
HADS (Effect of parent/caregiver)	X[a]			X[o]	X		X[s]		
BRIEF	X[a]			X[o]	X		X[s]		
QOLCE	X[a]			X[o]	X		X[s]		
Zarit Burden	X[a]				X		X[s]		
Subject Diary	C/R/D	C/R/D	R	C/R/D	C/R	X[t]	C/R/D	C/R	
Study Medication	D	C/R	R	C/R/D	C/R/D	C/R/D	C/R/D[k]	C/R	
Review Daily Diary Completion		---------- X ----------							
Concomitant Medication	X[a]	----------X----------							
Adverse Events	X[a]	----------X----------							
Adverse events of special interest	X[a]	----------X----------							X[l]

Abbreviations: AED=antiepileptic drug; BMI=body mass index; BRIEF=Behavior Rating Inventory of Executive Function; C=Collect; CBD=cannabidiol; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination; HADS=Hospital Anxiety and Depression Scale; QoL=quality of life; R=Review

a: Use data collected at Visit 12 of Part 1.
b: At the discretion of the Investigator, Visit 16 may be conducted as a phone visit.
c: Or early termination.
d: Safety Follow-up visits will be conducted for subjects who terminate early from Part 2 and for those who complete Part 2. Standard follow-up visits should occur 3 and 6 months after the last dose. For subjects enrolled in Germany, France and Netherlands, follow-ups will also occur 24 months after the last dose. If there are any findings at a post-dose follow-up, a follow-up visit will be scheduled every 3 months until resolved or stabilized.
e: Use Part 1 Visit 12 information unless complete neurological examination is warranted based on significant changes in subject status.
f: ECHOs will be performed at Months 1, 3, 6, and 9.

g: The Months 3, 6, 9, 15, 18, 21, 24, 27, 30, and 33 ECHO may be performed any time within 3 weeks prior to the study visit. If a subject discontinues early from the study, the ECHO should be scheduled as soon as practical.
h: Females of child-bearing potential
i: For Visit 15, use data collected at Part 1 Visit 12 unless clinical laboratory evaluation is warranted based on significant changes in subject status. For Visit 16, clinical laboratory evaluation is optional based on subject status.
j: Visit 20 only.
k: For subjects who are entering a different open-label trial for ZX008, do not initiate drug taper or conduct post-dosing and cardiac follow-up visits.
l: Only adverse events related to cardiac safety will be collected at this visit.
m: An abbreviated physical and/or neurological examination to be conducted as appropriate based on last exam and reported AEs.
n: Visits 19, 20, and 21 (Months 3, 6, and 9) only.
o: Visit 20 (Month 6) only
p: For subjects enrolled in Italy only: conduct routine EEG during Visits 15, 19, and 22
q: Visit 23 may be conducted as a phone call if physical and neurological examinations are not clinically indicated, provided diaries and study medication are returned by this time.
R Urine for urinalysis may be collected at home, the night before the clinic visit, as long as collection procedures are followed to maintain sample stability.
s As clinically indicated for Cohort B subjects extending Part 2 participation past 12 months. Abnormal clinically significant findings must be reported as adverse events
t After 12 months in Part 2, seizure diaries are not required for Cohort B. Rather, based on discussions with the parent/caregiver, clinical evaluation, and review of any documentation provided by the caregivers, investigators will assess the percent improvement in seizure burden on a 5-point scale: <25%, ≥25%, ≥50%, ≥75%, 100% [i.e., seizure-free] improvement.

** If ZX008 is not commercially available for the treatment of seizures associated with LGS after the end of the OLE Treatment Period, subjects may continue to receive ZX008 in a separate extension protocol. Continuation will be based on benefit/risk and will be offered to subjects who continue to meet eligibility requirements and comply with Investigator's instructions. For subjects who are entering a separate extension trial for ZX008, do not initiate drug taper or conduct post-dosing and cardiac follow-up visits.

The targeted study day and allowable windows for visits in Part 2 are reproduced from the protocol in Table 3.

Table 3: Visit Windows for Part 2 Visits

Cohort(s)	Visit / Procedure	Time window (relative to scheduled visit / procedure)
A and B	Visit 15 (Clinic; OLE Study Day 1)	± 4 days[a]
A and B	Visits 16 (Clinic/Phone; OLE Study Day 15)	± 3 days
A and B	Visits 17-21 (Clinic: OLE Study Days 30, 60, 90, 180, 270)	± 4 days
A and B	Visit 22 (Clinic; OLE Study Day 365; EOS for Cohort A)	± 4 days
A	Visit 23 (Clinic; OLE Study Day 379; post dosing)	± 4 days
A	Visit 24, 25 (ECHO clinic; 3-24 months after last dose[b])	+ 30 days
B	Visit 23-41 (Clinic/Phone; OLE Study Days 450, 540*, 630, 720*, 810, 900*, 990, 1080*, 1170, 1260*, 1350, 1440*, 1530, 1620*, 1710, 1800*, 1890, 1980*, 2070	± 4 days
B	Visit 42 (Clinic; OLE Study Day 2160; EOS) ± 4 days	± 4 days
B	Visit 43 (Clinic; OLE Study Day 2174; post-dosing) ± 4 days	± 4 days
B	Visit 44, 45 (ECHO clinic; 3 and 6 months after last dose) + 30 days	+ 30 days

Abbreviations: AED=antiepileptic drug (s); ECHO=echocardiogram
[a] In the case of a required safety review of a Visit 12 ECHO alert, the transition period between Visit 12 and Visit 15 may be extended up to 14 days to allow time for adjudication.
[b] Depending on country requirements.
*If marketing approval is not yet received after the end of the OLE Treatment Period, treatment may be extended on an annual basis in order to provide continuity of treatment for subjects who are enrolled in Part 2 of the study. Up to 5 annual extensions can be applied, for a total treatment time of 72 months in the OLE. Continuation will be based on review of safety/tolerability and effectiveness, and be offered for subjects who continue to meet eligibility requirements, comply with investigator's instructions, and for whom the investigator judges benefit outweighs risk. The decision to extend and informed consent should be completed before the start of the first visit of the extension (e.g., Month 12, 24, 36, 48 or 60). After approval from Investigator and Sponsor for extension and starting after Visit 26/ Month24 (or at a later visit if Visit 26/ Month 24 visit has already occurred at the time of Protocol Amendment 4.0 approval), subject will return to the clinic every 6 months for the 1 year extension (i.e., Month 30, 36). The End of Study will be Visit 42, unless another extension is granted, in which case the subject will continue to return for clinic visits every 6 months and will have a phone visit 3 months after the in-clinic visit. Further extensions can then be applied as required if marketing approval is not yet received.

4 Analysis Sets

Separate analysis data sets will be produced for Cohort A and Cohort B. Cohort A will include subjects from North America, Europe, and Australia; Cohort B will include subjects from Japan. The analysis sets used in Part 1 are defined in the final Statistical Analysis Plan for Part 1. The populations used in Part 2 are defined in this section.

4.1 OLE Safety Population (OLE SAF)

Safety analyses for Part 2 will be performed on the OLE Safety (SAF) Population, defined as all subjects who receive at least one dose of ZX008 during the open label extension.

4.2 OLE mITT Population

The OLE Modified Intent-to-Treat (mITT) Population is defined as all subjects who receive at least one dose of ZX008 and have a valid estimate of the frequency of seizures that result in drops from Part 1 and at least one month (30 days) of valid seizure data during the open label extension. Effectiveness analyses, such as evaluating the change in the frequency of drop seizures, will be performed on the OLE mITT Population.

4.3 Safety Population for Part 1 (DB SAF)

The SAF Population for Part 1 is defined as all randomized subjects who received at least one dose of ZX008 or Placebo in Part 1, regardless of entry into Part 2.

4.4 Long Term Safety (LT SAF)

This population will include subjects who received at least one dose of ZX008 during Part 1 or Part 2. For subjects treated with Placebo in Part 1 and who were treated with ZX008 in Part 2, the first dose of ZX008 would occur in the Part 1 transition period.

5 Endpoints

5.1 Efficacy Endpoints

The efficacy endpoints for Part 2 of the study are:

- The change from baseline in the frequency of seizures that result in drops (ESC confirmed).
- The change in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) between baseline and the OLE Treatment Period whether ESC confirmed as drop or not.
- The change from baseline in the frequency of all countable motor seizures (GTC, sGTC, TS, CS, AS, TA, FS, and HS)
- The change from baseline in frequency of all countable non-motor seizures (absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms).
- The change from baseline in the frequency of all countable seizures (i.e., motor and non-motor)
- The proportion of subjects who achieve a worsening from baseline (i.e., $\leq$0% reduction), or > 0%, ≥ 25%, ≥ 50%, ≥ 75%, 100% reduction, and "near seizure freedom" (i.e., 0 or 1 seizures) from baseline in frequency of seizures that result in drops (ESC confirmed), seizures that typically result in drops, all countable motor seizures, all countable non-motor seizures, and all countable seizures
- Number of seizure-free days, defined as 1) days with no seizures that result in drops (ESC confirmed) and 2) days with no countable motor seizures
- Longest interval between seizures that result in drops (ESC confirmed)
- Clinical Global Impression – Improvement rating, as assessed by the Principal Investigator.
- Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver
- Seizure Burden – Collected after Month 12 of OLE for subjects from Cohort B

5.2 Safety Endpoints

The safety endpoints for Part1 and Part 2 of the study are:

- AEs
- Laboratory safety (hematology, chemistry, urinalysis)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Body weight and BMI
- Physical examination
- Neurological examination
- BRIEF to measure changes in cognition of the subject
- Columbia Suicidality Severity Rating Scale (C-SSRS)
- 12-lead ECGs
- Doppler ECHOs
- Chest x-ray (for subjects enrolled in France and Netherlands only)

- EEG (for subjects enrolled in Italy only)

For public disclosure, only incidence of TEAEs will be publicly disclosed as a Secondary Endpoint for Part 1 and the Primary Endpoint for Part 2. The remaining Safety Endpoints are considered other for the purpose of public data Disclosure on ClinicalTrials.gov and EudraCT.

5.3 Exploratory Endpoints

The exploratory endpoints for Part 1 and Part 2 of the study are:

- The incidence of medical services used to treat seizures
- The incidence of status epilepticus
- Incidence of rescue medication usage
- Number of days rescue medication used
- The change from baseline in quality of life using the QOLCE
- The change from baseline in caregiver burden using the Zarit Caregiver Burden Inventory
- The change from baseline in affective symptoms of parent/caregiver using the HADS scale

6 Protocol Deviations

Major protocol deviations that occurred in Part 2 will be summarized using the OLE SAF Population. Major protocol deviations are those that have the potential to impact subject safety and/or affect data integrity and/or the efficacy conclusions. Major protocol deviations will be grouped into categories and may include categories such as:

- Non-compliance regarding intake of IMP
- Inappropriate intake of concomitant medication
- Subject not discontinued as per protocol
- Other non-compliance
- COVID-19 Related Deviations

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

Major protocol deviations will be presented in a subject data listing for the OLE SAF Population, sorted by site, subject, and study part.

Changes in study conduct due to COVID-19 will be summarized under the "COVID-19 Related Deviations" category. Any missed study visits, delayed study visits, or alternative study visits (e.g., telemedicine or phone call) will be summarized in a separate table.

7 General Aspects for Statistical Analysis

7.1 General Methods

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

Part 2 summaries may be presented by the subject's Part 1 treatment group (Placebo, ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day). As well, some summaries may be presented using the Part 2 categorized mean daily dosage, modal dose, and dosage at onset of certain events. See section 7.2.11 for the definition of mean daily dose and the categorization.

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

Point and interval estimates (95% confidence intervals) will be calculated for within treatment changes from baseline for key parameters as warranted. These within-treatment changes from baseline comparisons should be interpreted with caution, as any effect of treatment may be confounded with the time-course of disease or other factors. The primary evidence for efficacy and safety of ZX008 is based on the treatment comparisons from the Part 1 double-blind study, while the data from this OLE study provides evidence of long-term safety and effectiveness.

Confidence intervals and/or p-values, where provided for between treatment group differences, should be regarded as descriptive and not for formal inferential purposes.

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

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

7.2 Key Definitions

7.2.1 First Dose Date in Part 1

The first dose date will be assumed to be 1 day after the date of randomization.

7.2.2 First Dose Date in Part 2

The first dose date in Part 2 will be defined as the date of Visit 15.

7.2.3 Last Dose Date in Part 2

The last dose date in Part 2 is recorded on the Part 2 disposition Case Report Form (CRF) page. If this date is not populated, the last dose date will be derived from the daily dosing diary, using the last available date on or after the first dose date in Part 2.

7.2.4 Study Day

The Part 1 study day will be calculated relative to the First Dose Date in Part 1.

The Part 2 study day will be calculated relative to the First Dose Date in Part 2.

For any date on or after the date of first dose, study day will be calculated as assessment date – first dose date + 1. For any date prior to the date of first dose, study day will be calculated as assessment date – first dose date. There will be no Study Day 0.

7.2.5 Baseline Value (Part 1)

For non-seizure frequency assessments, the Part 1 baseline value will be the last non-missing assessment collected on or prior to the first dose date in Part 1.

Baseline values for seizure frequency endpoints will be determined from the immediate 28 days prior to Study Day 1 (i.e., the First Dose Date in Part 1) using methods described in the effectiveness section below.

7.2.6 Part 2 Baseline Value

The Part 2 Baseline value is defined as the last assessment, including unscheduled assessments, on or before the first dose in the OLE period. In most cases, except for the seizure frequency endpoints, this will be the value obtained at Visit 15.

7.2.7 Open-Label Extension (OLE) Treatment Period

For subjects in Cohort A, the OLE Treatment Period covers the 12 months during which subjects will receive open label treatment with ZX008, ending with the Cohort A End of Study (EOS) Visit or date of last dose of study drug, whichever occurs first. For subjects in Cohort B, the OLE Treatment Period may cover up to 72 months or until ZX008 is approved in a subject's country of residence and listed on a patient's health plan formulary.

7.2.8 Post-dosing Period

The Post-dosing Period begins immediately at the end of OLE Treatment Period and extends for 2 weeks.

7.2.9 Follow-up Period

Subjects are to return for an ECHO and ECG assessment 3 and 6 months after the last dose of study drug. Subjects enrolled in Germany, France, and Netherlands will have an additional 24 month follow-up. The follow-up period begins the day after the last dose and ends with Visit 25 (Cohort A) or Visit 42 (Cohort B).

7.2.10 Visit Windows and Period Start/Stop Dates

Table 4: Visit Windows and Period Start / Stop Dates

Phase	Period	Description
Pre-OLE Phase	Baseline (Part 1) Period	This period refers to the period prior to randomization in Part 1. The Baseline (Part 1) period start date is the date of Visit 1. The Baseline (Part 1) period end date is the date of Visit 3/randomization in Part 1.
Pre-OLE Phase	Part 1 T+M	The start date of this period is the date of randomization +1 day. The end date of this period is the last date the subject was on study treatment in Part 1.
Pre-OLE Phase	Part 1 Transition /Taper	This period includes the transition/taper period in Part 1.
OLE Phase	OLE Treatment Period	The OLE Treatment Period consists of the period from Visit 15 through the EOS/ET visit. The OLE Treatment Period start date is the date of first dose in Part 2. The OLE Treatment Period end date is the date of the EOS visit or the date of the last dose of study drug, whichever occurs first. For subjects who discontinue early from the study, the OLE Treatment Period end date will be the date of the ET visit - safety measures collected at the last clinic visit will be used even if study drug was discontinued prior to the date of the visit. Note: Adverse events on or after first dose in Part 2 are regarded as occurring during treatment. In addition, AEs occurring up to 30 days after the last dose date in Part 2 will be regarded as treatment emergent.
OLE Phase	OLE Taper Period	The OLE Taper period consists of 2 weeks starting from end of study/early termination visit + 1 day. The end date of this period is the date recorded for the Post-Dosing Visit.
Post-OLE Phase	Post-OLE Period	The start date of the post-OLE period is the date of the Post-Dosing Visit, + 1 day for subjects who complete the OLE Treatment period, or the day after the date of end of taper, for subjects who discontinue early and do not have a Post-Dosing Visit.

For the statistical analysis, visit windows around the target visit dates will be implemented to capture effectiveness and/or safety data within similar time frames. These windows are distinct from the permissible visit scheduling windows specified in the Visit Schedule in the protocol that are used for the conduct of the study.

The following rules will be used to window data into treatment periods for tabulations that are generated by time during the OLE Treatment period.

Table 5: Time Intervals for Analysis Visits for Seizure Analysis

Cohort(s)	Analysis Phase/Period	Scheduled Visit Number in Part 2	Analysis Visit*	Time Interval (label on output)	Time Interval (Day)
A and B	Pre-OLE	N/A	-99	Baseline (Part 1)	Part 1 Study Day -28 to Day-1 of Part 1
A and B	Pre-OLE	N/A	-9	Part 1 (T+M)	Day 1 of Part 1 to End of T+M in Part 1
A and B	Pre-OLE	N/A	-1	Part 1 Final Week	End of T+M in Part 1 – 6 days, to End of T+M in Part 1
A and B	Pre-OLE	N/A	-8	Part 1 Transition	End of T+M in Part 1 + 1 day to the Day before first Dose in Part 2
A and B	OLE	17	1	Month 1 (Part 2)	1-30
A and B	OLE	18	2	Month 2 (Part 2)	31-60
A and B	OLE	19	3	Month 3 (Part 2)	61-90
A and B	OLE	20	6	Month 4-6 (Part 2)	91-180
A and B	OLE	21	9	Month 7-9 (Part 2)	181-270
A and B	OLE	22 [#]	12	Month 10-12 (Part 2)	271-360
B	OLE	23	15	Month 13-15 (Part 2)	361-450
B	OLE	24	18	Month 16-18 (Part 2)	451-540
B	OLE	25	21	Month 19-21 (Part 2)	541-630
B	OLE	26	24	Month 22-24 (Part 2)	631-720
B	OLE	27	27	Month 25-27 (Part 2)	721-810
B	OLE	28	30	Month 28-30 (Part 2)	811-900
B	OLE	29	33	Month 31-33 (Part 2)	901-990
B	OLE	30	36	Month 34-36 (Part 2)	991-1080
B	OLE	31	39	Month 37-39 (Part 2)	1081-1170
B	OLE	32	42	Month 40-42 (Part 2)	1171-1260
B	OLE	33	45	Month 43-45 (Part 2)	1261-1350
B	OLE	34	48	Month 46-48 (Part 2)	1351-1440
B	OLE	35	51	Month 49-51 (Part 2)	1441-1530
B	OLE	36	54	Month 52-54 (Part 2)	1531-1620
B	OLE	37	57	Month 55-57 (Part 2)	1621-1710
B	OLE	38	60	Month 58-60 (Part 2)	1711-1800
B	OLE	39	63	Month 61-63 (Part 2)	1801-1890
B	OLE	40	66	Month 64-66 (Part 2)	1891-1980

Cohort(s)	Analysis Phase/Period	Scheduled Visit Number in Part 2	Analysis Visit*	Time Interval (label on output)	Time Interval (Day)
B	OLE	41	69	Month 67-69 (Part 2)	1981-2070
B	OLE	42 $	72	Month 70-72 (Part 2)	2071-2160
A	OLE	NA	99	Month 01-EOS (ENDPT1)	Day 1 to min(Last Dose date, up to EOS/ET Visit)
A	OLE	NA	100	Month 02-EOS (ENDPT2)	Day 31 to min(Last Dose date, up to EOS/ET Visit)
B	OLE	NA	101 ##	Month 01-Date of OLE Month 12 Visit	Day 1 to min(Last Dose Date, Last seizure diary date prior to or on Month 12 Visit Date or ET Visit Date)
B	OLE	NA	102 ##	Month 02-Date of OLE Month 12 Visit	Day 31 to min(Last Dose Date, Last seizure diary date prior to or on Month 12 Visit Date, ET Visit Date)

T+M=Titration + Maintenance in Part 1.
* Analysis visit numbers are not the same as nominal visit numbers.
# The End of Study (EOS) is at Visit 22 (per Protocol v. 3.1) for Cohort A.
$ The EOS is at Visit 42 (per Protocol 4.0) for Cohort B.
For Cohort B, the daily seizure diary and daily dosing diary are collected up to the date of the OLE Month 12 visit. Some subjects may have additional seizure diary entries after 12 months. That data will be tabulated but will not be included in the calculation of this endpoint.

Table 6: Time Intervals for Questionnaires*

Cohort(s)	Analysis Phase/Period	Scheduled Visit Number in Part 2	Analysis Visit Number*	Time Interval (label on output)	Time Interval (Study Day)	Target Time Point (Day)
A and B	Pre-OLE	N/A	-99	Baseline (Part 1)	≤ Part 1 Study Day 1*	Part 1 Day -28 – Part 1 Day 1*
A and B	Pre-OLE	15	-1	Baseline (Part 2)	1	Part 2 Study Day 1
A and B	OLE	17	1	Month 1 (Part 2)	21 to 44	30
A and B	OLE	18	2	Month 2 (Part 2)	45 to 74	60

Cohort(s)	Analysis Phase/Period	Scheduled Visit Number in Part 2	Analysis Visit Number*	Time Interval (label on output)	Time Interval (Study Day)	Target Time Point (Day)
A and B	OLE	19	3	Month 3 (Part 2)	75 to 134	90
A and B	OLE	20	6	Month 6 (Part 2)	135 to 224	180
A and B	OLE	21	9	Month 9 (Part 2)	225 to 314	270
A and B	OLE	22	12	Month 12 (Part 2)	>= 315 (Cohort A) 315 to 409 (Cohort B)	360
B	OLE	23†	15	Month 15 (Part 2)	410-484	450
B	OLE	24	18	Month 18 (Part 2)	485-574	540
B	OLE	25	21	Month 21 (Part 2)	575-664	630
B	OLE	26	24	Month 24 (Part 2)	665-754	720
B	OLE	27	27	Month 27 (Part 2)	755-844	810
B	OLE	28	30	Month 30 (Part 2)	845-933	900
B	OLE	29	33	Month 33 (Part 2)	934 - 1024	990
B	OLE	30	36	Month 36 (Part 2)	1025-1114	1080
B	OLE	31	39	Month 39 (Part 2)	1115-1204	1170
B	OLE	32	42	Month 42 (Part 2)	1205-1294	1260
B	OLE	33	45	Month 45 (Part 2)	1295-1384	1350
B	OLE	34	48	Month 48 (Part 2)	1385-1474	1440
B	OLE	35	51	Month 51 (Part 2)	1475-1564	1530
B	OLE	36	54	Month 54 (Part 2)	1565-1654	1620
B	OLE	37	57	Month 57 (Part 2)	1655-1744	1710
B	OLE	38	60	Month 60 (Part 2)	1745-1834	1800
B	OLE	39	63	Month 63 (Part 2)	1835-1924	1890
B	OLE	40	66	Month 66 (Part 2)	1925-2014	1980
B	OLE	41	69	Month 69 (Part 2)	2015-2104	2070
B	OLE	42	72	Month 72 (Part 2)	2105-2194	2160
A and B	OLE	OLE Last Visit***	99	Last Value	Day 2 to EOS date	

Note: For multiple measurements within a time window, please use the closest to the target time point. Note that measurements occurring on the end date of a phase/period or start date of a new phase/period are assigned to the preceding phase/period. For example, measurements taken on OLE Study Day 1 are assigned as Baseline (Part 2).
* Study day is relative to the first dose in Part 1. Otherwise, the study day is relative to the first dose in Part 2.
** The window applied here for Month 12 will differ depending on the Cohort. For Cohort A, the COVID-19 pandemic led to delays in the completion of Visit 22. Any collection for Cohort A on or after Day 315 are included in this window.
***The last observation collected in the study will be used.
† The only questionnaires administered during Visits 23-41 are seizure burden, C-SSRS and CGI-I (assessed by parent/caregiver and by investigator) are assessed during Visits 23-41.

7.2.11 Mean Daily Dose in Part 2 (mg/kg/day)

Diary-based Dose Calculation Method: The OLE mean daily dose for subjects in Cohort A and for the first 12 months in Part 2 for Cohort B will be determined from the mg/kg of study medication to be delivered

per day (e.g., 0.2 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg/day, 0.8 mg/kg/day), the subject's weight and the number of administrations per day recorded on the dosing diary. This is the time period where the daily dosing diary is collected. On each day, the actual dose will be calculated as:

1) Assigned dose level (mg/kg), if the subject's weight (kg) * assigned dose (mg/kg) was ≤ 30 mg or

2) 30 (mg) / weight (kg), if the subject's weight (kg) * assigned dose (mg/kg) was > 30 mg. The reasoning for this is that the maximum quantity to be given on any day is 30 mg.

3) 20 (mg) / weight (kg), if the subject was on concomitant STP and the subject's weight (kg) * assigned dose (mg/kg) was > 20 mg

4) On a day when incomplete dosing was completed (e.g., missed the morning dose, or took a partial evening dose), the actual dose will be prorated based on the portion of the full day's dosage the subject took. A partial dose will be considered as 25% of the subject's daily dosage.

The mean daily dose will be calculated as the sum of each day's dosage in mg/kg/day divided by the duration of OLE dosing.

Note that some subjects in Cohort B may have medication diary for more than 12 months in the OLE. Such data will not be used in the calculation of the mean daily dose. The Dispensation Record Calculation Method described below will be used to calculate the mean daily does for all Cohort B subjects after Month 12.

Dispensation Record Calculation Method: Subjects will not use a dosing diary after their first 12 months of participation in Part 2. Therefore, the mean daily dose after Month 12 will be calculated using study drug dispensation records rather than a diary. This calculation will assume 100% compliance. For example, let $Dose_1$ be a subject's initial dosage at the end of Visit 22 at Month 12. The subject will be assumed to take 100% of that dosage until there is a documented change in dosage assigned by the investigator, or until the first of either the Cohort B EOS/ET visit or the Treatment Termination Date. Let $Days_1$ be the number of days that the subject is assumed to be on that initial dosage. If a new dosage, $Dose_2$, is assigned, the subject will be assumed to continue at $Dose_2$ for the total number of days, $Days_2$, until another change in dosage is documented or the subject reaches the Cohort B EOS/ET visit or terminates treatment.

The mean daily dose for a subject is then calculated as:

$$[Dose_1 \times Days_1) + (Dose_2 \times Days_2) + \ldots. + (Dose_n \times Days_n)] / [Days_1 + Days_2 + \ldots + Days_n]$$

where $Dose_n$ and $Days_n$ are the last assigned dosage and number of days spent on the last assigned dosage, respectively.

End of treatment or study will be handled as follows:

- For subjects who have a Cohort B EOS or ET visit, the calculation will assume subjects stayed on their last assigned dose from the time it was assigned until either the date of the visit or the date of last dose), whichever is latest.
- Subjects who have not had an EOS or ET visit will be assumed to have been continuing treatment at the time of the cut-off date for any interim analysis.
- For subjects who are lost to follow up, the end of treatment date will be imputed with either the last dispense date + 180 days or the interim data-cutoff date, whichever is earliest.

For Cohort B subjects who remain in the OLE for more than 12 months, the mean daily dose for the entire time spent in the OLE will be the weighted average of the dose calculated using the Dosing Diary Method and the dose calculated by Dispensation Record Method.

For Cohort A, the mean daily dose will be categorized into 4 levels or 3 levels dependent on the analysis:

Four level categorization:

- 0 - < 0.2 mg/kg/day
- ≥ 0.2 - < 0.4 mg/kg/day
- ≥ 0.4 - < 0.6 mg/kg/day
- ≥ 0.6 mg/kg/day

Three level categorization:

- 0 - < 0.4 mg/kg/day
- ≥ 0.4 - < 0.6 mg/kg/day
- ≥ 0.6 mg/kg/day

Because of small number of patients in Cohort B, the mean daily dose will use only the three level categorization.

7.2.12 Mean Daily Dose in Part 2 (mg/day)

The OLE mean daily dose (mg/day) in Part 2 will follow the same logic described in the preceding section that derives the mean daily dose in mg/kg/day. However, the $Dose_i$ (i=1, 2, …, n) will be the assigned i-th dose multiplied by the weight collected most recently prior to the dispense or on the day of the dispense according to the CRF measurements.

This mean daily dose (mg/day) will be categorized:

- > 0 - ≤ 10 mg/day
- > 10 - <= 15 mg/day
- > 15 - < = 20 mg/day
- > 20 - <= 25 mg/day
- > 25 – <= 30 mg/day

7.2.13 Mean ZX008 Daily Dose in Part 1 and Part 2 (mg/kg/day)

For subjects in Cohort A, the ZX008 mean daily dose in Part 1 and Part 2 will be determined from the mg/kg of study medication to be delivered per day (e.g., 0.2 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg/day, 0.8 mg/kg/day), the subject's weight, and the number of administrations per day recorded on the medication diary using the Diary-based Dose Calculation Method described in the preceding Section 7.2.11.

For subjects in Cohort B, the Diary-based Dose Method will be used for Part 1 through the first 12 months of Part 2 when diary data is available. After 12 months, the Dispensation Record Calculation Method, described in Section 7.2.11, will be used. The mean daily dose for Part 1 through Part 2 will be the weighted average of the daily dose calculated using the Diary-based Method and the daily dose calculated using Dispensation Record Method.

For subjects treated with Placebo during Part 1 who transition into Part 2, the start of the ZX008 treatment period will start on the first dose in the transition period. For subjects treated with active ZX008 during Part 1, the start of their treatment period will start on the first dose date in Part 1.

This mean daily dose (mg/kg/day) will be categorized into four levels:

- 0 - < 0.2 mg/kg/day
- ≥ 0.2 - < 0.4 mg/kg/day
- ≥ 0.4 - < 0.6 mg/kg/day
- ≥ 0.6 mg/kg/day

7.2.14 Completed 6 Months of Part 2

For the statistical analysis, a subject will have been considered to have completed 6 months in Part 2 if they have completed treatment through Study Day 180 relative to the first dose in Part 2.

7.2.15 Completed 12 Months of Part 2

For the statistical analysis, a subject will have been considered to have completed 12 months in Part 2 if they have completed treatment through Study Day 361 (Study Day 365 – 4 day window) relative to the first dose in Part 2.

7.2.16 Completed Up to 6 Years in Part 2 for Cohort B

A subject in Cohort B will have been considered to have completed *n* (*n*=2, 3, …, 6) years in Part 2 if they have completed treatment through Study Day (365*n* – 4) relative to the first dose in Part 2. This makes the assumption that a subject has been ~~100%~~ compliant with their study medication until the investigator has documented the subject's last Part 2 study drug date.

7.2.17 Completed Part 2

For the statistical analysis, a subject in Cohort A or Cohort B will have been considered to have completed Part 2 if they have completed the Visit 22 visit within or after the Month 12 visit window. If marketing approval is not yet received by Visit 22, treatment may be extended on an annual basis to provide continuity of treatment. Up to 5 annual extensions can be applied, for a total treatment time of 72 months in the OLE. Participation after Visit 22 is not considered when determining whether a subject is a Part 2 completer.

7.3 Missing Data

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 Adverse Event Start and End Dates

Missing start and end date will be imputed conservatively, i.e., missing values will be imputed in such a way that the duration of the AE is considered with the longest possible duration and such that, whenever the AE may potentially start after first date of study medication in Part 2, the AE will be handled as a treatment-emergent adverse event (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 definitions given in the following table.

Table 7: Handling of Partial Dates in Adverse Events

	Adverse event
Partial /Missing Start date	Missing day – If adverse event day is missing but month and year is present then impute the 1st of the month unless month is same as month of first dose of study drug in Part 1, then impute first dose date in Part 1. Missing day and month – If adverse event day and month are both missing but year is present then impute 1st January unless year is the same as first dose date in Part 1 then impute first dose date in Part 1. Completely missing – impute first dose date in Part 1 (if reported during Part 1) or Part 2 (if reported during Part 2) unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date. When imputing a start date, ensure that the new imputed date is sensible i.e., is prior to the end date of the AE.

Partial /Missing End date	Missing day – If the AE end day is missing but month and year are present then impute the last day of the month unless month is same as month of last dose of study drug in Part 2 then impute last dose date in Part 2. Missing day and month – If the AE has missing day and month but year is present then impute 31st December unless year is the same as first dose date in Part 2 then impute last dose date in Part 2. Completely Missing – Evaluate whether the AE is still ongoing and AE Start Date in relation to first dose of study drug. If the ongoing flag is missing then assume that AE is still present (i.e., do not impute a date). If the AE has stopped and start date is prior to first dose date, then impute the 1st dose date. If the AE started on or after the first dose date, then impute the last dose date.

Data Handling for Seizure Diaries

Seizures are recorded in the Daily Seizure Diary (DSD) for the entire Part 2 duration for Cohort A and the first 12 months of Part 2 for Cohort B. The DSD asks subjects/caregivers to either report a seizure or confirm that the day has been seizure free. There will be no explicit imputation of intermittent missing data for seizure diaries. Missing seizure diary data will be handled as follows:

If no seizures are entered in the DSD on a particular day and the response to the question, is there a seizure to report that day, is "No, this day has been seizure free" then that day will have the seizure count set to 0.
If seizures are entered in the DSD and the response to the question, is there a seizure to report that day, is "No this day has been seizure free" the seizures entered in the DSD will supersede the seizure freedom affirmation.
If no seizures are entered in the DSD on a particular day and there is no response to the question, is there a seizure to report that day, that day will be considered to have missing diary data.
If no seizures are entered in the DSD on a particular day and it is indicated that there were seizures that day, that day will be considered to have missing diary data.

7.4 Pooling of Centers

If feasible, some analyses may pool data from Cohorts A and B combined.

7.5 Subgroups

The following subgroups may be utilized for effectiveness analyses and adverse event summarizations as indicated:

- Age (using age at the start of Part 1): 2– < 6 years, 6–< 12 years, 12 - < 18, 2-< 18 years, ≥ 18 – 35 years, < 15 years, ≥ 15 years
- Sex: Male, Female
- Race: White, non-White
- Baseline Weight group (using weight at the start of Part 1): < 35 kg, 35-70 kg, > 70 kg
- Region (applicable only to Cohort A): Subjects from North America, Europe, Australia
- Number of concomitant AED medications used in Part 2 (categorized): ≤ 2, 3, ≥ 4
- Number of AED medications taken prior to the start of Part 1~~: 0-3, 4-6, 7-9, ≥ 10~~
- Name/type of three concomitant AED medications most commonly used in Part 2 Cohort A: valproate, clobazam, and common combinations of AEDs
- Name/type of three concomitant AED medications most commonly used in Part 2 Cohort B: rufinamide, topiramate, valproic acid

Not all subgroups will be used in the interim analyses. See Section 17 for a complete list of the tables, listings, and figures produced for interim analyses.

8 Demographic, Other Baseline Characteristics and Medication

8.1 Subject Disposition and Withdrawals

The Part 2 subject disposition will be presented per treatment received in Part 1 and overall, for Cohort A and B independently. If reasonable, some analyses may be performed using data from Cohorts A and B combined.

For describing the Part 2 subject disposition, the following will be summarized by number and percentage:

- Subjects in OLE Safety Population
- Subjects in OLE mITT Population
- Subjects assigned to OLE Safety Population, OLE mITT Population, who discontinued the study and reason for discontinuation.
- Completed 6 months in Part 2
- Completed 1 year in Part 2
- Completed Part 2
- Completed 2 years in Part 2
- Completed 3 years in Part 2
- Completed 4 years in Part 2
- Completed 5 years in Part 2
- Completed 6 years in Part 2

The denominator used to calculate the percentage will be the number of subjects in the OLE Safety Population or OLE mITT Population, as applicable. For Cohort A, disposition will be summarized by region as well.

The number and percentage of subjects who discontinue, together with the primary reason for discontinuation, will be presented by the number of years of participation in the OLE. For example, a subject who discontinues at Month 26 will be tallied with other subjects who discontinue after Month 24 but before Month 36. The total number and percentage of subjects and reasons for discontinuation will also be presented.

All subject disposition data will be listed using the OLE Safety Population and the OLE mITT Population.

8.2 Demographic and Other Baseline Characteristics

Subject demographics and baseline characteristics will be summarized descriptively per treatment received in Part 1 and overall, for the OLE Safety Population for Cohort A and B. If reasonable, some analyses may be performed using data from Cohorts A and B combined. If the OLE mITT Population is

different than the OLE Safety Population, then the summaries will be repeated for the OLE mITT Population.

For Cohort A, the demographic characteristics will be summarized separately by region (North America, Europe, and Australia)

The following demographic characteristics will be summarized:

- Age at entry into Part 1 [Years]
- Categorized Part 1 age as: For Cohort A: 2 - < 6 years, ≥ 6 - < 12 years; ≥ 12 - < 18 years, ≥ 18 – 35 years; For Cohort B: 2 - < 18 years, ≥ 18 – 35 years; 2 - < 15 years, ≥ 15 – 35 years
- Age at entry into Part 2 [Years]
- Categorized Part 2 age as: For Cohort A: 2 - < 6 years, ≥ 6 - < 12 years; ≥ 12 - < 18 years, ≥ 18 – 36 years; For Cohort B: 2 - < 18 years, ≥ 18 – 35 years; 2 - < 15 years, ≥ 15 – 36 years
- Sex
- Race
- Ethnicity
- Part 1 Baseline Height [m]
- Part 2 Baseline Height [m]
- Part 1 Baseline Weight [kg]
- Part 1 Baseline Weight Categorized as: < 37.5 kg vs. ≥ 37.5 kg
- Part 2 Baseline Weight [kg]
- Part 2 Baseline Weight Categorized as: < 37.5 kg vs. ≥ 37.5 kg
- Part 1 BMI [kg/m^2]
- Part 2 BMI [kg/m^2]
- Geography (Cohort A only): North America (including USA, Canada, Mexico), Europe, Australia

All subject demographics data will be listed for the OLE Safety Population.

8.3 Medications and Treatments

Prior AEDs are described and coded as noted in the Part 1 SAP. Prior AEDs will be extracted from Part 1 eCRFs.

Concomitant medication (collected on the concomitant medications eCRF page) will be coded using the World Health Organization Drug Dictionary (WHO-DD) Format B3 Version Sep2017. Non-medication treatment/therapies are recorded on the Concomitant non-medication eCRF. The therapies recorded on the non-medication pages will not be coded to a dictionary.

Concomitant AEDs (collected on the concomitant AED eCRF page) will be coded using the WHO-DD Format B3 Version Sep2017 or later. Anti-epileptic medications will be identified using any drug entered with the ATC2 level code of “Antiepileptics”.

The following algorithm will be used to define concomitant in Part 2.

Concomitant medications in Part 2 will be defined as those medications that were initiated on or after the first dose date in Part 2 or those medications that started before Part 2 and were ongoing on or after the first dose date in Part 2.

If the start date or stop date of a medication is partially missing, the date will be compared as far as possible with the first dose date in Part 2. The following approach will be taken:

- If the start date occurs prior to the first dose date in Part 2 but the end date is missing on or after the first dose date in Part 2, the medication will be considered concomitant in Part 2.
- If the start day is missing but the start month and year are complete, a medication will only be excluded as being concomitant in Part 2 if the start month/year is before the month/year of first dose date in Part 2 and if the stop date (either full date, month, and year if missing day, or year if missing month and day) is before first dose date in Part 2.
- 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 the first dose date in Part 2 and if the stop date (either full date, month, and year if missing day, or year if missing month and day) is before the first dose date in Part 2.
- If the start date is completely missing and the stop date is prior to first dose in Part 2, the medication will be assumed to be a prior medication in Part 2.

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

Part 2 medication summary tables will be presented for the OLE SAF Population. Concomitant medications and therapies/treatments and concomitant antiepileptic medications will be defined and analyzed for the OLE SAF Population. Concomitant medications/treatments and concomitant antiepileptic medications will be listed for the OLE SAF Population.

Rescue medications are medications listed as provided as needed in association with a seizure event. They are also recorded on the Rescue Medication eCRF. A Part 2 concomitant rescue medication is a rescue medication recorded in the seizure diary that is used in relation to a seizure event date recorded on or after the first dose date in Part 2.

Note that further summaries of rescue medications recorded on the daily medication diary are described in the effectiveness section.

8.4 Seizure History

A listing of seizure types experienced by each subject will be provided. All seizure types experienced by the subject prior to and during the study are included, as well as new seizure types that were experienced in Part 2.

9 Safety

All Part 2 safety analyses will be performed for the OLE Safety Population, as defined in Section 4.1, unless noted otherwise. Analysis results for Part 2 from Cohort A and B will be compared through descriptive statistics and if reasonable, some analyses may be performed using data from Cohorts A and B combined.

9.1 Extent of Exposure

9.1.1 Part 2 Exposure Duration

Duration of exposure in Part 2 in days will be calculated as:

Date of last IMP intake in Part 2 – Date of first full daily IMP intake in Part 2 + 1

The Part 2 exposure duration in days will be summarized using the OLE Safety Population by the mean daily dose given in Part 2 using summary statistics: n, mean, standard deviation, median, minimum, Q_1, Q_3 and maximum. This exposure will also be summarized by subgroups of Part 1 Age Group (groups specified in Section 8.2), ~~and for Cohort A only,~~ sex, Part 1 weight subgroup, and the number of concomitant AED drugs used during Part 2.

The Part 2 Exposure duration will be summarized categorically by the Part 2 mean daily dosage (mg/kg/day), breaking the duration into 30-day monthly periods (≤ 1 month, 31 – 60 days = > 1 - ≤ 2 months, 61 – 90 days = > 2 - ≤ 3 months, up to 24 months. After 24 months, the duration will be presented in yearly intervals (e.g., > 24 - <= 36 months, > 36 months - < 48 months, etc. Similarly, the Part 2 Exposure duration will be summarized categorically by the Part 2 mean daily dosage, measured in (mg/day).

For the OLE Safety Population, the cumulative duration in days in Part 2 that the subject was assigned to a specific dosage will be summarized. Due to the Open-Label dosing, the periods where the subject is assigned to a particular dose are not necessarily consecutive. As an example, a subject may be assigned to 0.4 mg/kg/day during Month 2 – Month 3, 0.2 mg/kg/day during Month 3 – Month 6, and 0.4 mg/kg/day from Month 6 onward.

For the OLE Safety Population, the shift in dosage of ZX008 will be presented at each scheduled visit starting from Visit 17 – OLE Month 1 through End of Study. For each visit, the number of subjects who attended the visit will be provided, and those subjects will be summarized by the dosage of ZX008 assigned at the last study drug dispensation prior to the visit and the dosage of ZX008 assigned at the conclusion of the visit.

9.1.2 ZX008 Combined Part 1 and Part 2 Exposure Duration

Combined treatment exposure to ZX008 during double-blind through open label treatment periods will be summarized for all subjects treated with ZX008 during Part 1 and/or Part 2. This will include: 1) any subject treated with active ZX008 during the double-blind period, 2) any subject treated with active

ZX008 during the taper/transition of Part 1, and/or 3) any subject treated with ZX008 during Part 2 of the study.

This duration will be calculated as:

The duration of Part 1 treatment exposure + the duration of Part 2 treatment exposure – 1 day (if the last dose date in Part 1 = the first dose date in Part 2) if the subject was randomized to active ZX008 in Part 1.

The duration of treatment during the transition period in Part 1 + the duration of treatment in Part 2 – 1 day (if the last dose date in Part 1 = the first dose date in Part 2) if the subject was randomized to Placebo in Part 1.

The ZX008 combined Part 1 and Part 2 exposure duration will be summarized with descriptive statistics using the LT SAF Population by the mean daily dose in Part 1 and Part 2. The ZX008 combined Part 1 and Part 2 exposure duration also will be summarized categorically, breaking the duration into cumulative periods (≥ 30 days, ≥ 3 months, ≥ 6 months, ≥ 1 year, and for Cohort B, also ≥ 2, ≥ 3, ≥ 4, ≥ 5, and ≥ 6 years)

9.2 Treatment Compliance (Diary and Bottle Weight)

Study medication is to be administered twice daily, and self-reported compliance is recorded in the eDiary, per dose, as full (full dose consumed), partial (less than full dose consumed) or missed (no dose consumed) each day. From this, compliance will be calculated by assuming that a missed dose=0% of BID dose consumed, partial=50% of BID dose consumed, and full=100% of BID dose consumed. For each subject, a daily diary compliance score will be thus obtained.

Compliance will also be determined based on the actual quantity taken, determined using the weight of the dispensed drug kits and weight of the returned drug kit. The expected quantity taken will be determined using the assigned dosage in mg/kg/day and the number of days they were assigned at that dosage. If a kit was not returned, the compliance for the period will be missing.

For Part 2, compliance will be summarized for the OLE SAF and OLE mITT Populations. Compliance for Part 2 will be derived for the first 12 months of Part 2 using the DSD-based assessment. Compliance for Part 1 through the first 12 months of Part 2 will be determined and summarized using the Safety Population for Part 1.

Compliance values will be categorized as:

- < 80%
- 80% - < 90%
- 90% - < 100%
- 100% - < 110%
- ≥ 110%

9.3 Adverse Events

An AE is defined as any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, and whether considered related to the medicinal (investigational) product.

A TEAE in Part 2 is defined as any AE with an onset on or after the first dose date in Part 2. AEs with onset in Part 1 that are ongoing in Part 2 are not included in the count of AEs in Part 2.

The original terms used by the investigators in the eCRFs to identify AEs will be coded using the MedDRA Version 20.1 or later.

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

The severity of AEs (for both nonserious and serious AEs) will be assessed by the investigator as described in Section 9.3.1.

9.3.1 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 AE with missing severity will be imputed as "severe."

9.3.2 Treatment Emergent Adverse Events

Summaries of TEAEs will be provided for the OLE Safety Population, unless noted otherwise.

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

- TEAE
- Related TEAE
- Serious TEAE
- Related serious TEAE
- Severe TEAEs
- Severe related TEAE

- Adverse event of special interest
- TEAEs leading to premature discontinuation of study treatment
- TEAEs leading to premature discontinuation from the study
- Death

This overview summary table will be presented for the full Part 2 period. The summary will be performed by the study drug dosage of ZX008 at onset in Part 2 and using the mean daily dose and modal dose used during Part 2.

The following summaries in Part 2 will display the number and percentage of subjects with an adverse event by system organ class (SOC) and preferred term (sorted alphabetically):

- All TEAEs
- Serious TEAEs
- Study Drug Related TEAEs
- TEAEs by Maximum Severity
- All TEAEs leading to premature discontinuation from the study
- All TEAEs leading to premature discontinuation from treatment

These summaries will be presented for the full Part 2 period. The summary will be performed by study drug dose at the time of adverse event onset in Part 2 and using the mean daily dose used during Part 2. Selected summaries will also be performed by the modal daily dosage during the study.

Summaries of TEAEs will be summarized by study drug dose at the time of adverse event onset in Part 2 for the following subgroups for Cohort A:

- Part 1 Age: 2– < 6 years, 6–< 12 years, 12 - < 18, ≥ 18 years.
- Sex
- Three most common concomitant AEDs used by Cohort A in Part 2

Summaries of TEAEs will be summarized by study drug dose at the time of adverse event onset in Part 2 for the following subgroups for Cohort B:

- Part 1 Age: 2 - < 18 years, ≥ 18 years; 2 - < 15 years, ≥ 15 years.
- Sex
- Three most common concomitant AEDs used by Cohort B in Part 2

Using the LT Safety Population, the summary of TEAEs by treatment received in Part 1 will also be performed using Cohort A subjects who used Valproate during Part 2 (valproate magnesium, valproate sodium, valproate semisodium, valproate sodium/valproic acid, or valproic acid) vs. those who did not.

Using the LT Safety Population, a similar summary of TEAEs by treatment received in Part 1 will be performed using Cohort A subjects who used Clobazam during Part 2 vs. those who did not.

Using the LT Safety Population, analyses of Part 2 TEAEs by treatment received in Part 1 will be summarized for Cohort A subjects using the most common combinations of AEDs used versus those subjects who did not use the combination.

Using the LT Safety Population, a summary of the most commonly occurring adverse events (≥ 5% [Cohort A] or ≥ 10% [Cohort B] incidence overall or in the dose at onset column) in Part 1 through Part 2 while receiving active ZX008 will be provided by dosage at onset, first showing the number of subjects, number of events (noting that a subject may have multiple occurrences of the same event), and the number of resolved events. Another summary of the most commonly occurring adverse events (≥ 5% [Cohort A] or ≥ 10% [Cohort B] incidence overall or in the dose at onset column) will be completed showing the showing the mean time to first event (measured from the date of first ZX008 treatment) and the mean duration of the event. For subjects who have multiple occurrences of the same event during the study, the first event will be used in the summary. For unresolved events, the duration will be calculated using the last date of follow-up.

Using the OLE Safety Population, a summary of the most commonly occurring adverse events in Part 2 (≥ 5% [Cohort A] or ≥ 10% [Cohort B]) incidence overall or in the dose at onset column) will be provided, first showing the number of subjects, number of events (noting that a subject may have multiple occurrences of the same event), and the number of resolved events. Another summary of the most commonly occurring adverse events (≥ 5% incidence overall or in the dose at onset column) will be completed showing the showing the mean time to first event (measured from the date of first dose in Part 2) and the mean duration of the event. For subjects who have multiple occurrences of the same event during the study, the first event will be used in the summary. For unresolved events, the duration will be calculated using the last date of follow-up.

For the OLE Safety Population, a summary of the most commonly occurring adverse events in Part 2 (≥ 5% [Cohort A] or ≥ 10% [Cohort B] incidence overall or in the dose at onset column) will be presented by mean daily dose, modal dose, and the most recently assigned dosage level prior to the onset of the event.

For the OLE Safety Population, a summary table of adverse events with onset during Part 1 that were ongoing at the start of Part 2 will be provided summarizing by the treatment received during Part 1.

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.

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 or treatment
- Deaths
- Ongoing AEs with onset during Part 1 for subjects in the OLE Safety Population
- AEs from Part 1 and Part 2 for subjects in the Long Term Safety Population

9.3.3 Adverse Events of Special Interest (AESI)

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

Table 7 – Adverse Events of Special Interest:

Metabolic/Endocrine
1.Elevated prolactin level ≥2x above the upper limit of normal (ULN)
2.Hypoglycemia – <3.0 mmol/l or 54 mg/dl, whether that level is associated with symptoms or not
Neuropsychiatric
1.Suicidal thoughts, ideation or gestures

For Part 2, adverse events of special interest (AESI) will be summarized by system organ class and preferred term. The summary will be performed by study drug dose at the time of AE onset, mean daily dose, and the modal dose.

All AESIs occurring in Part 2 will be listed separately.

For results disclosure on public registries (e.g., ClinicalTrials.gov), treatment-emergent adverse events and treatment-emergent serious adverse events will be included.

9.4 Physical Examination and Neurologic Examination

During Part 2, a complete physical and neurologic examination will be performed for Cohort A at Visit 15, Visit 22, and Visit 24, if applicable. An abbreviated physical and neurologic examination is performed at Visit 16 and 23, and as appropriate based on the previous exam or AE findings.

For Cohort B, a complete physical and neurological examination will be performed at Visit 15, 22, and 42, if applicable. An abbreviated physical and neurologic examination is performed at Visit 16, 21, 23-41, and 43, if clinical indicated, and as appropriate based on the previous exam or AE findings.

A listing will be presented showing whether physical and neurologic examinations were abnormal or not.

9.5 Vital Signs, Weight, and BMI

During Part 2, vital signs data are scheduled to be documented at each clinic visit from Visit 15 through End of Study according to the schedule provided in Table 2. The measurements will include blood pressure, heart rate, temperature, respiratory rate.

During Part 2, body weight is scheduled for collection at each clinic visit according to the schedule provided in Table 2. Height is scheduled for collection at Visit 15 and Visit 22 for Cohort A and at Visit 15, 22, and 42 for Cohort B. BMI will be calculated as weight (kg) / height $(m)^2$. At visits where the height is not collected BMI will be determined using the most recently collected height value. For Cohort A, age- and sex-based Z-scores for height and weight at each assessment will be determined using growth charts available from the Centers for Disease Control (CDC) and the World Health Organization (WHO). Details of the data sources are available at the following website.

https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm

The z-scores will be determined based on the subject's age at the date of assessment. For subjects with an incomplete birth date due to country requirements, January 1st of the provided year of birth will be assumed to be the date of birth. The z-scores will be determined only for subjects whose age at assessment is < 18 years of age. For Cohort B, the Japanese Growth Standard Chart 2000 from the Japanese Society for Pediatric Endocrinology is used as the reference to calculate the z-scores.

For each vital sign, observed values and change from Part 2 baseline and change from Part 1 baseline to each on-study evaluation will be summarized.

For weight, the occurrence of at least a ≥ 7% gain/reduction or ≥ 10% gain/reduction from Part 1 and/or Part 2 baseline will be summarized for the OLE Safety Population by visit and at any time during Part 2. Weight summaries will also be presented by age group (2 to <18 years and >= 18 years for Cohort B).

For subjects with an occurrence of a ≥ 7% reduction in weight from Part 1/Part 2 baseline, spaghetti plots will be produced for the OLE Safety Population detailing the subjects value of weight over time to assess the recovery from weight loss. For Cohort B, the plots will be presented by subgroups of subjects 2 to < 18 and ≥ 18 years of age.

~~Correlations between weight loss and decreased appetite will be performed.~~

Vital signs, weight, height, and BMI data will be presented in a data listing. For each subject with a clinically meaningful abnormality in vital signs (provided in Appendix 3), a table will be produced organized by parameter that lists each subject, age, sex, and day of abnormal value.

9.6 Electrocardiogram

Analysis of ECGs will be included in a separate report from Clario (formerly ERT, Biomedical Systems).

9.7 Doppler Echocardiography

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

9.8 Tanner Staging

In Part 2, Tanner Staging will be assessed for subjects > 7 to 18 years old according to the schedule of assessments given in Table 2.

Conceptually, pubertal maturation can be described in terms of sequence, timing, and tempo. Puberty consists of a series of predictable events, and the sequence of changes in secondary sexual characteristics has been categorized by several groups. The 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 separately for boys and girls overall and broken out for the following Part 1 age groups:

> 7 years to ≤11 years,

> 11 years to ≤ 15 years,

> 15 years to ≤ 18 years.

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

9.9 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 analyzed:

- Hematology: hemoglobin, hematocrit, erythrocytes, erythrocyte mean corpuscular volume, leukocytes, erythrocyte mean corpuscular hemoglobin, erythrocyte mean corpuscular hemoglobin concentration, neutrophils, lymphocytes, monocytes, eosinophils, basophils platelets, and mean platelet volume
- Chemistry: albumin (ALB), alkaline phosphatase (AP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bicarbonate, blood urea nitrogen (BUN), calcium (Ca), chloride (Cl), creatinine, creatine kinase, gamma-glutamyl transferase (GGT), glucose, lactate dehydrogenase (LDH), phosphate, potassium (K), sodium (Na), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, urate, eGFR, IgG, IgA, IgM.

- Tests of growth and precocious puberty: insulin-like growth factor-1 (IGF-1, low sensitivity), prolactin, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), testosterone, estradiol, Total T3, Total T4, TSH, somatotrophin
- Coagulation: Prothrombin time (PT), International normalized ratio (INR), activated partial thromboplastin time (PTT) (listing only)
- Urinalysis: analysis for pH, glucose, ketones, nitrite, protein, bilirubin, urobilinogen, leukocyte esterase, and occult blood. Microscopic analysis will be performed for red blood cells, all cell types, and casts.
- Pregnancy test: Urine or serum pregnancy testing will be performed in female subjects of childbearing potential (listing only)
- Urine or serum THC panel, whole blood cannabidiol (listing only)

At each scheduled assessment, and at the last post-baseline assessment in Part 2, the observed and the change from Part 1 baseline in the continuous laboratory data will be descriptively summarized by type of laboratory test/parameter.

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

For each continuous laboratory parameter, shift tables will be created comparing the Part 1 baseline status with the status at each post-baseline visit. Status will be classified as:

- below lower limit of normal
- within normal limits
- above upper limit of normal

Listings of the most extreme values for a subject recorded in Part 2 will be created for each parameter. These will show the lowest recorded value and the highest recorded value noted for the subject. For Cohort A, a listing of subjects with markedly abnormal laboratory results will be provided. For Cohort B, a listing of subjects with critically high or low abnormal laboratory results will be provided. Additional explorations of the data may be conducted as warranted.

9.10 Columbia-Suicide Severity Rating Scale

During Part 2, the Columbia-Suicide Severity Rating Scale (C-SSRS) data will be collected at each clinic visit from Visit 15 through end of study, as displayed in Protocol PA 3.1 Table 2 for Cohort A, and Protocol PA 4.0 Table 2 for Cohort B.

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.

An electronic tablet will be used to collect C-SSRS data and will only ask about a subject's capability to complete C-SSRS during the Baseline visit. If the site records that the subject is incapable of answering the questions, the C-SSRS will be removed from their list of required questionnaires for the remainder of the study.

All individual subject C-SSRS data will be listed.

[redacted]

The following o [redacted] ses (yes/no):

Category	
1	[redacted]
2	
3	
4	
5	

[redacted] is assessed as a "yes" answer at any time during the d to any one of the five ques icidal ideation will be presente at least once during the OLE Treatment period.

[redacted]

The following o s for [redacted] and have binary responses (yes/no):

Category	
6	[redacted]
7	
8	
9	
10	

[redacted] is assessed as a "yes" answer at any time during the OLE Treatment period to any one of the five ques the number and percentage of subjects who had suicidal behavior will be presented. The denominator will be the number of subjects completing the C-SSRS at least once during Part 2.

[redacted]

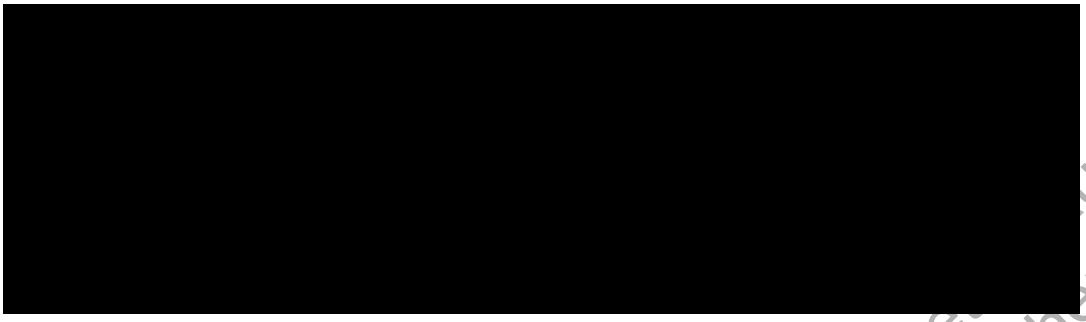
An overall composite will be provided similar to the [redacted] endpoints, but will instead count a subject if any of the C-SSRS questions 1 through 10 are marked as 'yes' any time during Part 2.

[redacted]

For Part 2, the number and percentage of subjects having reported any time during the Part 2 experiencing a [redacted] event (Question 11) will be provided using the OLE Safety Population.

A shift table of the subject's Part 1 baseline categorization (No [redacted]) vs. the subject's most severe Part 2 categorization will be provided using the OLE Safety Population. The denominator used for the calculation of percentages will be the number of subjects who completed the C-SSRS prior to Part 1 and who had the C-SSRS completed at least once

[redacted]



10 Effectiveness

The analysis of the Part 2 effectiveness parameters will be performed on the OLE mITT Population for Cohort A and B independently. If reasonable, some analyses may be performed using data from Cohorts A and B combined. Summaries of effectiveness will typically be broken out by Part 1 blinded treatment assignment and presented for all subjects combined. Select effectiveness measures will also be summarized for groups defined by the mean daily dose of ZX008 taken in Part 2. No inferential tests will be used to compare treatment or dose groups.

10.1 Primary Effectiveness Endpoint and Analysis

The calculation of the primary effectiveness endpoint depends on DSD, which is not required after the first 12 months in Part 2. Therefore, this section is applicable for only the first 12 months in Part 2. Regarding the percent improvement burden endpoint after 12 months in Part 2 Cohort B, refer to Section 10.6 of this SAP.

10.1.1 Drop Seizure Effectiveness Endpoint Definition

The first effectiveness endpoint is the change from baseline in the frequency of seizures that result in drops (DSF) per 28 days. The following seizure types from the DSD will be included in the frequency count of seizures resulting in drops, if for an individual subject, the seizure as listed in the eCRF has been confirmed and approved by the Epilepsy Study Consortium (ESC) as a 'drop seizure':

- atonic seizures [AS]
- tonic seizures [TS]
- tonic/atonic seizures [TA]
- generalized tonic-clonic seizures [GTC]
- secondarily generalized tonic-clonic [SGTC]

To aid in assessing the effectiveness of OLE treatment with ZX008 after treatment with blinded fixed doses in Part 1, DSF per 28 days will be presented for all subjects in the OLE mITT Population, by the Part 1 Treatment group, and by Part 2 Mean Daily Dose for the Part 1 baseline period, the T+M period of Part 1, the last week in double-blind treatment (T + M), the transition period of Part 1, the entire OLE treatment period, and separately for the first, second and third months of the OLE. For Cohort A, the DSF over the remainder of the OLE treatment period will also be presented, for 3-month intervals. For Cohort B, DSF will be reported at Months 6, 9, and 12, and at ensuing 3-month intervals for any subjects who continued to use seizure diaries past Month 12. The next section defines variables associated with these endpoints.

Two key DSF-related variables will be defined. For Cohort A, these are:

(1) the difference in drop seizure frequency per 28 days (DSF) for the open-label Treatment Period (Part 2 Day 1 to Cohort A EOS) compared to the Baseline (Part 1);

(2) the difference in DSF for Month 2 to Cohort A EOS (Part 2 Day 31 to Cohort A EOS) time point compared to the Baseline (Part 1).

The two key DSF-related variables for Cohort B are defined as follows:

(1) the difference in drop seizure frequency per 28 days (DSF) during the first 12 months open-label Treatment Period (Part 2 Day 1 to Visit 22 or ET, whichever comes first) compared to the Baseline (Part 1);

(2) the difference in DSF for Month 2 to Month 12 (Part 2 Day 31 to Visit 22 or ET, whichever comes first) compared to the Baseline (Part 1).

The frequency of drop seizures during a given interval will be derived from the number and type of events recorded in subject diaries. For each subject, the seizure frequency per 28 days will be calculated as the number of seizures recorded during the period, divided by the number of days in the period and multiplied by 28. The drop seizure frequency will be calculated from all available data collected during the relevant interval.

The frequency of drop seizures will be counted from the daily diary records provided by the Subject or Parent/Caregiver.

Responses to the DSD question about the number of seizures per seizure episode will be handled differently according to the following response options.

Response	**Number of seizures**
No seizures	0
A single seizure	1
An episode of many discrete seizures	Based on the subject/caregiver response in the DSD to the triggered question “Enter the number of seizures in the episode”.
A cluster of seizures back-to-back	This will be determined empirically using the data reported for “episodes of many discrete seizures” of other subjects in the study as described below.

Seizure Clusters

Seizure clusters without a perceptible interictal period (i.e., “back-to-back”) that are entered in the DSD were considered uncountable and only the duration of the event is recorded in hours: minutes: seconds. For a cluster of seizures back-to-back the number of discrete seizures that occurred during a cluster is not entered in the DSD. To estimate the number of seizures during a back-to-back cluster, the number of

seizures will be imputed using the seizure count and duration of seizures recorded for "an episode of many discrete seizures".

Specifically, episodes of many discrete seizures include both an estimate of the number of seizures, and an estimate of the duration of the seizures in the episode, categorized into 1 of 3 duration "buckets": <2 minutes; 2-10 minutes; >10 minutes.

The median number of discrete seizures reported in the discrete seizure cluster events across all Cohort A subjects in the Part 1 T+M period will be used to impute the number of seizures experienced during a cluster of back-to-back seizures in Part 2. The definition defined here uses the Part 1 T+M period to maintain comparability between the Part 1 summaries and the Part 2 summaries, that is, to ensure that Parts 1 and 2 both use the same number when imputing the number of seizures in a back-to-back cluster.

The median number of seizures will then be used to impute counts for seizure clusters:

- 'short' clusters (i.e., ≤ 59 minutes) will be assigned the median number of seizures reported in discrete seizure events <2 minutes
- 'medium' clusters (i.e., 1-5 hours) will be assigned the median number of seizures reported in discrete seizure events 2-10 minutes
- 'long' clusters (i.e., > 5 hours) will be assigned the median number of seizures reported in discrete seizure events > 10 minutes.

An alternative method for imputation of the number of seizure events associated with episodes that were described in the eDiary as "A cluster of seizures back to back" will be performed. The "A cluster of seizure back-to-back" episodes are those that did not have a number of seizure events associated with them. In order to associate a number of seizure events associated with them, the following alternative method for imputation will be used.

1.) Cluster episodes described in the diary as "A cluster of seizures back-to-back" will be classified according to duration, as in the primary analysis.

- Short: < 1 hour duration
- Medium: 1 – 5 hours, inclusive
- Long: > 5 hours

2.) Seizure cluster episodes described as "An episode of many discrete seizures" that occurred during the Titration or Maintenance Period of Part 1 will be identified as in the primary analysis. These episodes were reported in the diary with information about the number of discrete seizures in the cluster episode and the duration of a single discrete seizure within the cluster episode.

3.) The duration of a single seizure within the discrete seizure cluster episode will be defined as:

- 2 minutes, if the duration of the discrete seizure was answered as "Less than 2 minutes"
- 10 minutes, if the duration of the discrete seizure was answered as "2 – 10 minutes"
- 15 minutes, if the duration of the discrete seizure was answered as "More than 10 minutes"

4.) The total duration of the overall discrete seizure cluster episode will be calculated as the duration from step 3 multiplied by the number of seizures reported in the discrete seizure cluster episode.

5.) The total duration from step 4 will be categorized into categories as:

- Short: <= 59 minutes
- Medium: 60 minutes – 300 minutes (i.e., 1 – 5 hours, inclusive)
- Long: > 300 minutes

6.) The median number of seizures reported within a discrete seizure cluster episode will be determined for all discrete cluster episodes in the Short, Medium, and Long discrete cluster duration categories in the population. The median value will then be imputed into the Short, Medium, and Long duration back-to-back cluster categories.

The frequency of ESC-confirmed drop seizures will then be determined using the alternative cluster event imputation. The summary statistics, nonparametric model, and parametric models as used for the primary endpoint will be used for the cluster event sensitivity analysis.

Drop Seizure Frequency Calculation

The Baseline (Part 1) drop seizure frequency, or DSF_{B1}, is calculated as in Part 1, using the DSF from the 28 consecutive days immediately preceding the date of Part 1 Day 1. For any individual subject, the frequency of seizures that result in drops – the drop seizure frequency for short – per 28 days during the baseline period (DSF_{B1}) will be derived as follows:

$$DSF_{B1} = \frac{28 \times \text{Total number of drop seizures during the Part 1 baseline period}}{\text{Total number of days in the Part 1 study baseline period with nonmissing diary data}}$$

The drop seizure frequency per 28 days for Part 1 T+M period (DSF_{TM}) is defined below:

$$DSF_{TM} = \frac{28 \times \text{Total number of drop seizures during the Part 1 T + M period}}{\text{Total number of days in the Part 1 T + M period with nonmissing diary data}}$$

The drop seizure frequency per 28 days for the Part 1 Final Week of T+M (DSF_{FW1}) is defined below:

$$DSF_{FW1} = \frac{28 \times \text{Total number of drop seizures during the final week of Part 1 T + M}}{\text{Total number of days with nonmissing diary data during the final week of Part 1 T + M}}$$

The drop seizure frequency per 28 days for the Part 1 transition period of Part 1 (DSF_{TRA}) is defined below:

$$DSF_{TRA} = \frac{28 \times \text{Total number of drop seizures during the days in the Part 1 transition period}}{\text{Total number of days with nonmissing diary data during the Part 1 transition period}}$$

The transition period will be defined as the day after the end of the Part 1 Maintenance period to the day before the first treatment in Part 2.

Additionally, for Cohort A, for the other intervals (Month 1 through Cohort A EOS) defined in Table 5, the drop seizure frequency per 28 days for that interval, $DSF_{OLE, I}$, i=1, 2, 3, … , 12, is defined as follows:

$$DSF_{OLE, i} = \frac{28 \times \text{Total number of drop seizures in the } i\text{th interval}}{\text{Total number of days in the } i\text{th interval with nonmissing diary data}}$$

The two key effectiveness measures for Cohort A, DSF_{E1} and DSF_{E2}, will be calculated as follows:

$$DSF_{E1} = \frac{28 \times \text{Total number of drop seizures from Day 1 of OLE to Cohort A EOS}}{\text{Total number of days from Day 1 to Cohort A EOS with nonmissing diary data}}$$

$$DSF_{E2} = \frac{28 \times \text{Total number of drop seizures from Day 31 of OLE to Cohort A EOS}}{\text{Total number of days from Day 31 to Cohort A EOS with nonmissing diary data}}$$

The two key effectiveness measures for Cohort B, DSF_{BE1} and DSF_{BE2}, will be calculated as follows:

$$DSF_{BE1} = \frac{28 \times \text{Total number of drop seizures from Day 1 of OLE to Visit 22}}{\text{Total number of days from Day 1 to Visit 22}}$$

$$DSF_{E2} = \frac{28 \times \text{Total number of drop seizures from Day 31 of OLE to Visit 22}}{\text{Total number of days from Day 1 to Visit 22}}$$

10.1.2 Drop Seizure Effectiveness Endpoint Definition Analyses

In all seizure analyses, the Baseline (Part 1) value will be the baseline used. For any of the variables defined in the previous section, the change from baseline for any individual subject will be calculated as:

CDSF = Post-baseline value – DSF_{B1}

The percentage change from baseline for any individual subject will be calculated as:

PCDSF = (Post-baseline value – DSF_{B1}) *100 / DSF_{B1}

The key effectiveness measures are the medians of $PCDSF_{E1}$ and $PCDSF_{E2}$. Summary statistics for the changes from baseline, and the percentage changes from baseline will also be presented. A Wilcoxon signed-rank test will be used to assess the significance of the percentage change from baseline. Given that baseline refers to the period prior to initiation of double-blind treatment in Part 1, it is expected that long-term treatment with ZX008 will lead to a reduction in drop seizure frequency. If we designate the Part 1 baseline DSF, DSF_{E1}, DSF_{E2} by μ_{B1}, μ_{E1}, and μ_{E2}, respectively, the key effectiveness objective is to test the null hypothesis listed as the following:

H_0: $\mu_{E1}-\mu_{B1}=0$,

Against the alternative:

H_A: $\mu_{E1}-\mu_{B1}\neq 0$,

Rejection of the null hypothesis in favor of the alternative, in the presence of a statistically significantly smaller drop seizure frequency during OLE Treatment (two-sided p-value < 0.05) will be regarded as evidence of a treatment benefit.

For both Cohorts A and B, a graph of the median DSF for Part 1 baseline, and during the months of the OLE period will be generated by treatment received during Part 1, and another graph of the percentage changes from baseline may be plotted.

For Cohort A, subgroup analyses by Part 1 Age Group, Part 1 Baseline Weight, Sex, Geographic Region, Number of Prior AED Medications, Number of Concomitant AED medications, and Baseline Frequency of Seizures Resulting in Drops will be produced. For Cohort B, subgroup analyses by Part 1 Baseline weight and Age Group (2 to < 18 vs. ≥ 18 years, and 2 to < 15 vs. ≥ 15 years) will be produced.

10.2 Additional Seizure Counts

The other effectiveness endpoints of change in the frequency per 28 days between Part 1 Baseline and OLE Period:

- All Typical Drop Seizures (i.e., GTC, SGTC, TS, AS, TA regardless of ESC confirmed as drop or not)
- All Countable Motor Seizures
- All Countable Non-Motor Seizures
- All Countable Seizures

Each of these endpoints will be calculated using the same method as the drop seizure endpoint. The OLE mITT Population will be used for these analyses.

In addition, change in the frequency per 28 days between Part 1 Baseline and OLE Period of all countable seizures that do not result in drops (i.e., Non-Drop seizures) will be analyzed in the same manner.

Refer to Appendix 19.1 for the seizure types that are included in each of these endpoints. Not all types of seizures will be analyzed in interim analyses. See Section 17 for a complete list of the tables, listings, and figures produced for interim analyses.

10.3 Percentage Change from Baseline in Seizure Frequency

For each of the seizure types noted (seizures resulting in drops, typical drop seizures, all countable motor seizures, all countable non-motor seizures, all countable seizures, and all countable seizures that do not result in drops), a response curve will be generated for the OLE mITT Population. The graphs will plot the % of subjects (y-axis) against percentage reduction from Part 1 baseline in seizure type frequency per 28 days in the OLE treatment period (x-axis). In the graph, subjects experiencing an increase in seizure frequency will be regarded as having a 0% reduction in drop seizure frequency. Hence the ordinate for the time point = 0 may not necessarily be at 100%. The graph will be generated for all subjects. Not all graphs will be generated for interim analyses. See Section 17 for a complete list of the tables, listings, and figures produced for interim analyses.

In each seizure type, a point estimate and 95% CI for the % of subjects experiencing a worsening or no change (≤ 0% reduction), > 0% reduction, ≥ 25% reduction, ≥ 50% reduction, ≥ 75% reduction, 100% reduction, and near seizure-freedom (0 or 1 seizures) will be computed. For both Cohorts A and B, the reductions will be computed from the Part 1 baseline to Month 1, Month 2, Month 3, Month 4-6, Months 7-9, Month 10-12, Month 13-15, Month 16-18, and Month 19-21. In addition, reductions will be presented for Cohort A for the Month 1- Cohort A EOS and Month 2 to Cohort A endpoints. For Cohort B, reductions will be presented for the Month 1 – Month 12 and the Month 2 to Month 12 endpoints. An exact 95% Clopper-Pearson CI for each proportion will be presented.

10.4 Seizure-Free Days

Seizure-free days will be taken from the parent/caregiver diary data.

A seizure-free day with no seizures leading to drops will be defined as a day for which diary data are available and with no ESC-defined drop seizures. A seizure-free day with no seizures that typically lead to drops will be defined as a day for which diary data are available and with no seizures that typically lead to drops. A day without countable motor seizures will be defined as a day for which diary data are available and with no countable motor seizures. For Cohort A, the total numbers of countable motor seizure-free days, typical drop seizure days, and drop seizure-free days will be summarized using descriptive statistics by Part 2 mean daily dose for the Month 1 – EOS of OLE Period and the Month 2 – EOS of the OLE period. For Cohort B, the total numbers of countable motor seizure-free days, typical drop seizure days, and drop seizure-free days will be summarized using descriptive statistics by Part 2 mean daily dose for the Month 1 – Month 12 of the OLE Period and the Month 2 – Month 12 of the OLE period.

Seizure-free days per 28 days at Part 1 baseline = (number of seizure-free days during baseline period)*28/ (number of days during baseline with non-missing diary data)

For Cohort A, seizure-free days per 28 days during Month 1 – EOS in the OLE Period = (number of seizure-free days during Month 1 to EOS in OLE Period)*28/ (number of days during Month 1 - OLE Period with non-missing diary data).

For Cohort A, seizure-free days per 28 days during Month 2 – EOS in OLE Period = (number of seizure-free days during Month 2 to EOS in OLE Period)*28/ (number of days during Month 2 - OLE Period with non-missing diary data).

For Cohort B, Month 12 refers to the date of Visit 22 or ET, whichever comes first. For Cohort B, seizure-free days per 28 days during Month 1 – Month 12 in the OLE Period = (number of seizure-free days during Month 1 to Month 12)*28/ (number of days during Month 1 – Month 12 with non-missing diary data).

For Cohort B, seizure-free days per 28 days during Month 2 – Month 12 in OLE Period = (number of seizure-free days during Month 2 to Month 12)*28/ (number of days during Month 1 – Month 12 with non-missing diary data).

A Wilcoxon signed-rank test will be used to assess the significance of the percentage change from baseline in seizure-free days.

10.5 Duration of the Longest Interval between Seizures Resulting in Drops

The duration of longest interval between seizures resulting in drops (in days) will be analyzed using nonparametric methods.

For each subject in Cohort A, the duration of the longest interval between seizures resulting in drops (i.e., ESC confirmed) will be calculated over the entire OLE period. This will be derived as the maximum of the number of consecutive days between seizures resulting in drops. The length of the intervals between seizures resulting in drops will be calculated as below, after which the duration of the longest interval between drop seizures will be derived.

For each subject in Cohort B, the duration of the longest interval between seizures resulting in drops (i.e., ESC confirmed) will be calculated over the first 12 months of the OLE period. For this analysis Month 12 refers to the date of Visit 22 or ET, whichever comes earlier. This will be derived as the maximum of the number of consecutive days between seizures resulting in drops. The length of the intervals between seizures resulting in drops will be calculated as below, after which the duration of the longest interval between drop seizures will be derived.

If a subject has a missing diary day within an otherwise seizure-free interval, the current seizure-free interval will end on the first date of missing diary data, and a new one begun on the next date with available diary data where no seizure occurs. In that case, for purpose of calculation of this variable, all intervening days with missing diary data, will be assumed to have a drop seizure occurrence, until the first available date with non-missing diary data.

Let Date0 (=Day1) be the first day of treatment. If a seizure resulting in a drop 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 OLE period, where LDT ≥ Date5, then the time interval between 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 interval between seizures resulting in drops (in days) will be presented for the OLE mITT Population as a whole. Additional summary statistics will be presented, including mean, minimum, maximum, 25th percentile, and 75th percentiles. The change from baseline in the length of the longest interval will be assessed using a Wilcoxon signed-rank test.

A boxplot summarizing the duration of the longest interval between seizures will be provided.

10.6 Seizure Burden Assessment in Cohort B

After 12 months in Part 2, seizure diaries are not required. Rather, based on discussions with the parent/caregiver, clinical evaluation, and review of any documentation provided by the caregivers, investigators will assess the percent improvement in seizure burden on a 5-point scale: <25%, ≥25%, ≥50%, ≥75%, 100% [i.e., seizure-fee] improvement. Assessments will be made at 3-month intervals for subjects in Cohort B beginning at Visit 23 (Month 15).

The number and percentage of Cohort B subjects in each of the five categories will be presented for Visit 23 and for each subsequent visit. A two-sided 95% CI will for each percentage using the Clopper-Pearson method be calculated. In addition, the number of subjects who had at least a ≥25% improvement – i.e., the number who had either a ≥25%, ≥50%, ≥75%, or 100% improvement, – will be presented along with its associated percentage and CI. Similar tallies will present the number of subjects with at least a ≥50% improvement and the number with at least a ≥75% improvement.

10.7 Clinical Global Impression – Improvement (CGI-I) Rating, as assessed by the Principal Investigator

The Principal Investigator will rate their global impression of the subject's condition at each clinic visit after randomization. During Part 2, it is assessed at every in-clinic visit except Visit 16.

The CGI-I scale measures the change in the subject's clinical status from a specific point in time, i.e., the Part 1 Baseline Period. The CGI-I rating scale permits a global evaluation of the subject's improvement over time. The severity of a subject'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

At each assessment time point during the OLE Treatment period, frequency counts (and %) of scores, by severity rating will be produced overall, and by Part 1 treatment group.

Descriptive statistics will be presented for the following dichotomized categories for each time point and will include the number and % of subjects responding in the combined categories, along with an associated exact two-sided 95% CI:

- (1) Very much improved or much improved, i.e., number of subjects with a score of 1 or 2;
- (2) Improved, i.e., number of subjects with a score of 1, 2, or 3

This will be presented for the OLE mITT Population as a whole and by Part 1 treatment group. For Cohort A, subgroup analyses of the CGI-I by Part 1 Age Group, Sex, and the number of concomitant antiepileptic medications, will be produced. For Cohort B, CGI-I will be analyzed as a whole and by Part 1 Age Group. Analyses by other subgroups may also be produced. A graphic showing the percentage of respondents in each category at last assessment in Part 2 will be presented.

Individual subject data will be listed for the CGI-I scale as assessed by the investigator.

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

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

10.9 Exploratory Effectiveness Endpoints and Analyses

10.9.1 Incidence of Status Epilepticus

For Cohort A and for the first 12 months that subjects spend in Cohort B, the incidence of status epilepticus (SE) will be evaluated based on 1.) cases captured as those entered as adverse events (including SAEs) into the safety database, and as 2.) seizures lasting longer than 10 min (single seizures, seizures within a discrete cluster, or duration of an uncountable/back-to-back cluster) from the seizure diary. A single seizure meeting more than one of these sources will be counted once.

A sensitivity analysis of SE cases reported from the seizure diary meeting the following criteria will be completed. Only seizure events classified into any of the following types will be counted.

- Generalized tonic-clonic (GTC)
- Secondarily generalized tonic-clonic (SGTC)
- Focal with clear observable signs
- Focal without clear observable signs
- Absence / atypical absence

For the primary analysis, the number and percentage of subjects with SE recorded as an AE during the Part 1 baseline period and the OLE period will be presented by the Part 2 mean daily dose and overall. The number of episodes of SE and descriptive statistics for the number of episodes and episode rate per 28 days will be provided. The episode rate will be determined by counting the number of events and dividing by the number of days in the period where a seizure diary was completed and multiplying this fraction by 28. In addition, from the diary data, the number and percentage of subjects having seizures with duration >10 min during OLE, the number of episodes and episode rate per 28 days will be reported by the Part 2 mean daily dose and overall. Finally, the number and percentage of subjects having events from the diary and/or AE database will be summarized by the Part 2 mean daily dose and overall.

For the sensitivity analysis of seizure events that were GTC, SGTC, Focal with clear observable signs, Focal without clear observable signs, or absence / atypical absence, the number and percentage of subjects with SE reported during the Part 1 baseline period and for the OLE period will be presented by the Part 2 mean daily dose and overall. The number of episodes of SE and event rate per 28 days will be provided for the following groups of events.

Each SE event for the sensitivity analysis will be further classified into the following events:

- All episodes
- Episodes with no rescue medications administered
- Episodes with 1 rescue medication administered
- Episodes with more than 1 rescue medication administered

Daily records of seizures will not be available for subjects in Cohort B after the first 12 months of participation in the OLE. Therefore, the SE analyses described above cannot be performed for subjects in Cohort B after 12 months. Instances of SE will continue to be recorded as AE and will be presented in AE summary tables. The summary of SE for Cohort B subjects will be limited to the period from the start of the OLE period to Month 12 of the OLE period.

10.9.2 Rescue Medication Usage

For subjects in Cohort A and for the first 12 months that subjects spend in Cohort B, the use of rescue medication is recorded on the daily diary. For this analysis, in Cohort B, Month 12 will be the date of Visit 22 visit or ET, whichever comes earlier. In the event of prolonged seizures or status epilepticus, rescue medication may be 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 different medications or different doses than the first round of rescue meds.

The incidence (Yes/No) of use of rescue medication and the number of days rescue medication was taken (normalized to 28 days) and change from Part 1 baseline for post-baseline time points will be summarized for the Baseline (Part 1), Month 1, Month 2, and Month 3, Month 4-6, Month 7-9, and Month 10-12 of the OLE Treatment Period, and the complete Part 2 OLE Treatment Period by the mean (SD) as well as the median and range. Data will be summarized by Part 2 mean daily dose. Statistical significance of the within group median change from baseline will be assessed using a Wilcoxon signed-ranks test.

A categorical analysis of the change from Part 1 baseline in the number of days where rescue medication was taken (normalized to 28 days). Data will be summarized by Part 2 mean daily dose and overall using the OLE mITT Population. The number of rescue medications used per status epilepticus episode recorded on the seizure diary will be summarized using similar descriptive statistics as above. Rescue medications are related to an episode of SE recorded on the seizure diary.

10.9.3 Incidence of Medical Services

Data on hospitalization and healthcare resource use will be captured in the CRF and will be used to calculate incidence.

Details of the hospitalizations, including reasons for hospitalization and use of resources for the entire study (Part 1 and Part 2) will be provided in a listing. The number and percentage of subjects who utilized medical center care will be summarized by Part 1 Treatment and overall.

10.9.4 Quality of Life in Childhood Epilepsy (QOLCE) Scale

The parent/caregiver completed the QOLCE. This assessment looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, well-being, cognition, social activities, behavior, and general health (Sabaz et al., 2000; Talarska 2007). There is also one question on overall quality of life, administered as part of the QOLCE.

In Part 2, the QOLCE is scheduled to be collected at Visit 15, Visit 20, and Visit 22 ([End of Study for Cohort A or Month 12 for Cohort B]/Early Termination). Assessments may be performed at additional visits for some subjects. All QOLCE data will be listed. Assessments will be mapped to an analysis visit, based on the windows defined in Section 7.2.10, Table 6.

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. [Details of the reverse coding are provided in the shells for the TLFs]. Item scores will then be transformed to a 0-100 scale as follows: 1 -> 0, 2 -> 25, 3 -> 50, 4 ->75, 5 -> 100. After transformation, a score for each subject for each subscale is calculated by averaging that subject's responses to each item in the subscale. A value of 0 represents the lowest or poorest score and 100 reflects the highest level of functioning. The 16 subscale scores per subject are then averaged to obtain an overall quality of life score for each subject.

A higher subscale and overall quality of life score, indicates a better response.

Table 8: Subscale of QOLCE

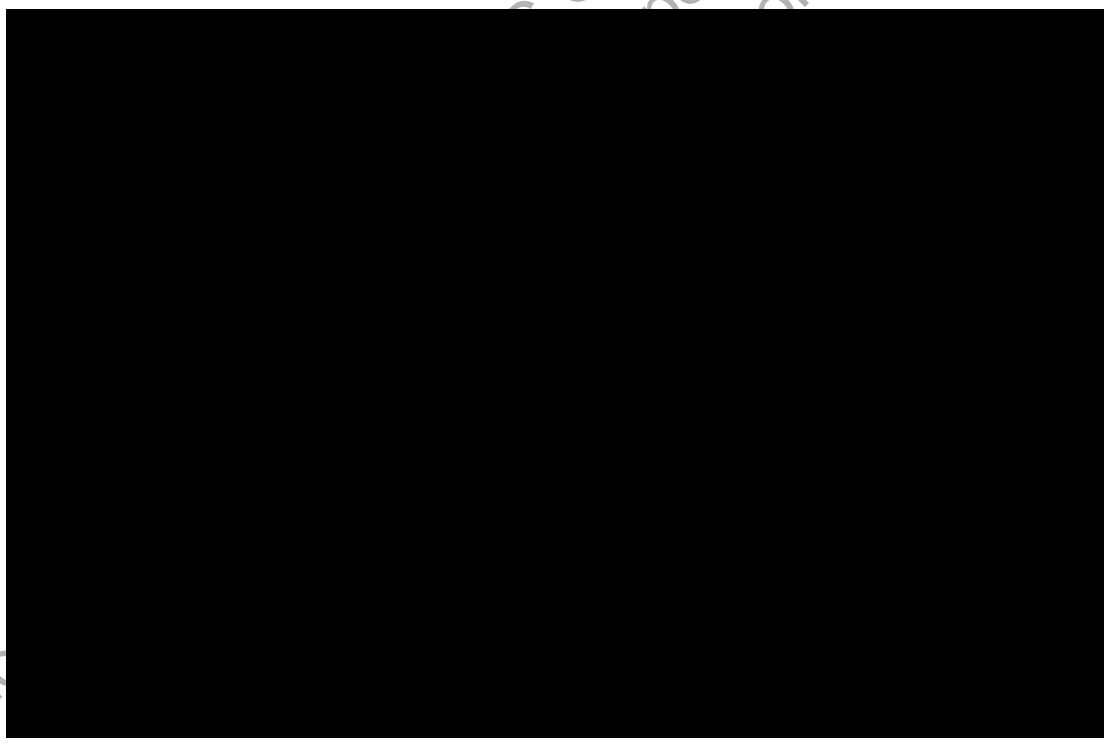
Domain	Subscale	Item
Section 3: Physical	Physical Restrictions	3.1 a-j
Section 3: Physical	Energy/Fatigue	3.2 a,b
Section 4: Well-being	Depression	4.1 a,d,e,l
Section 4: Well-being	Anxiety	4.1 b,g,j,n,o,p
Section 4: Well-being	Control/helplessness	4.1 c,f,h,i
Section 4: Well-being	Self-esteem	4.1 k,m,q,r,s
Section 5: Cognition	Attention/Concentration	5.1 a,d,e,f,g
Section 5: Cognition	Memory	5.1 j,k,l,m,n,o
Section 5: Cognition	Language	5.1 p,q,r,s,t,u,v,w
Section 5: Cognition	Other Cognitive	5.1 b,c,h
Section 6: Social Activities	Social Interactions	6.1 c,f,h
Section 6: Social Activities	Social Activities	6.1 a, e, 6.2
Section 6: Social Activities	Stigma Item	6.1 i
Section 7: Behavior	Behavior	7.1 a, c,f,g,h,i,j,k,l,m,o,q,r,s,t
Section 8: General Health	General Health	8.1

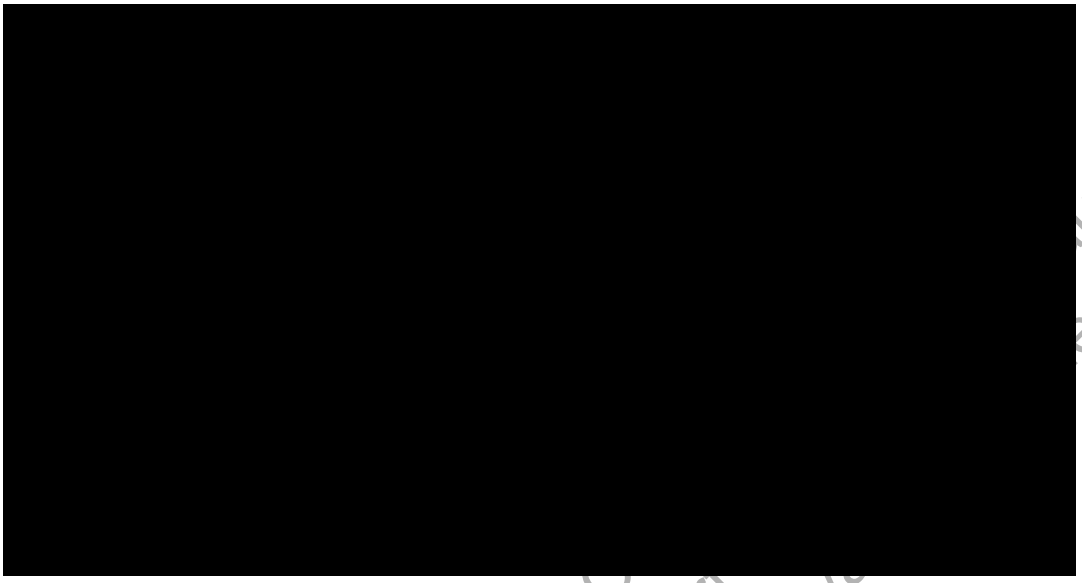
Section 2 (USA Version) or Section 9 (Australia Version): Quality of Life	Quality of Life Item	2.1 or 9.1
Overall Quality of Life *		Average of 16 subscale scores*

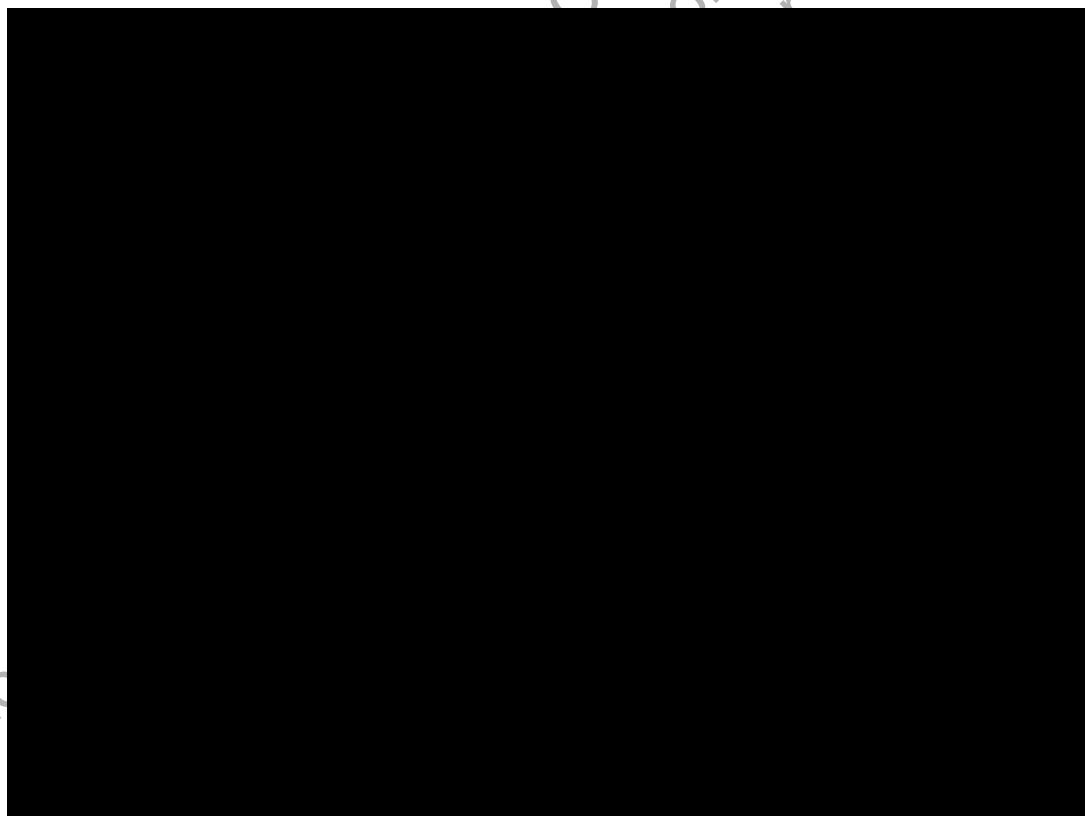
*An Overall Quality of Life Score will be computed by adding each subscale score for each individual and then dividing by 16.

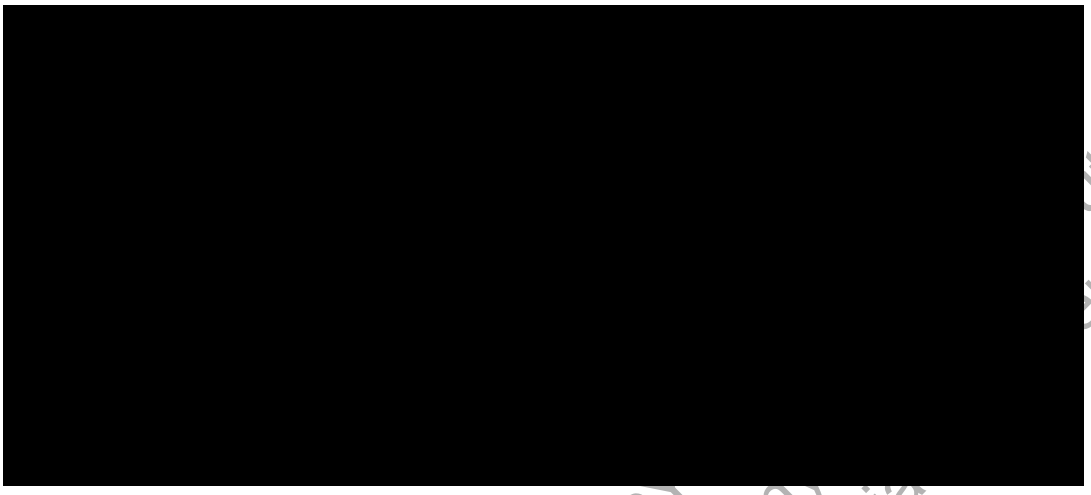
At each analysis visit, the descriptive statistics, including the n, mean, standard deviation, median, minimum, and maximum will be generated for each QOLCE subscale and for the overall quality of life score. Summaries will be provided overall and by treatment received during Part 1.

In addition, the change from Part 1 baseline in the overall QOLCE will be calculated for each subject by subtracting the Part 1 baseline score from the score measured at each scheduled post-baseline visit. Statistical significance of the within group median change from baseline will be assessed using a Wilcoxon signed-ranks test.









11 Exploratory Analyses due to COVID-19

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

12 Interim Analyses

12.1 Interim Analysis for Supplemental New Drug Application (sNDA)

12.1.1 Overview

COVID-related issues and precautions have delayed the completion of ZX008-1601 Part 2 for an indefinite period. Many subjects have either been unable or unwilling to complete their final visit, and travel restrictions have impeded monitoring visits. Given the uncertainty in predicting when the trial can be completed, an interim analysis of Part 2, Cohort A will be performed to generate the data summaries and analyses needed to support an sNDA regulatory submission. This sNDA interim analysis will be based on a snapshot of the clinical database taken on 19 October 2020 – a date chosen to ensure that the analysis includes at least 365 ± 4 days of exposure in Part 2 for greater than 90% of subjects in Cohort A. The analysis will comprise a large subset of the tables, listings and figures planned for the final analysis of Cohort A. A full list of the tables, listings and figures included in the interim analysis is given in Sections 17 and 18.

12.1.2 Safety Analyses

The primary purpose of the sNDA interim analysis is the same as for Part 2: to assess the long-term safety and tolerability of ZX008 in children and adults with LGS. As such, the interim analysis will include all safety tables, listings and figures planned for the final analysis of Cohort A including all tables and listings that summarize AEs, laboratory assessments, vital signs, weight, BMI, physical and neurological exams, ECHO, ECG, C-SSRS data, IMP treatment exposure/dosage data, compliance with IMP intake, Tanner staging, and BRIEF questionnaire summaries.

12.1.3 Effectiveness Analyses

Since effectiveness measures are secondary objectives of this open-label extension, fewer effectiveness analyses will be included in this interim analysis than are specified for Part 2 as a whole. Specifically, the sNDA interim analysis will focus on effectiveness measures related to the primary and key secondary seizure-related endpoints used to evaluate efficacy in the pivotal, Part 1 portion of the trial. These include analyses of:

- the frequency of seizures that result in drops (ESC-confirmed) and that do not result in drops,
- the proportion of subjects who attain 50% or greater decrease in seizures that result in drops (ESC-confirmed) and that do not result in drops, as well as a worsening or no change (i.e., ≤ 0% reduction), > 0%, ≥ 25%, ≥ 75%, 100% reduction, or near drop seizure freedom (i.e., 0 or 1 seizure) from Baseline
- the number of drop seizure-free days (ESC-confirmed and Typical Drops)
- the longest interval between seizures that result in drops (ESC-confirmed and Typical Drops)

Analyses of the effectiveness measure related to the non-seizure related Part 1 key secondary endpoint, the Clinical Global Impression – Improvement rating as assessed by the Principal Investigator, will also be performed for the OLE mITT Population overall and by Part 1 age subgroup. The Clinical Global Impression – Improvement rating as assessed by the parent/caregiver will also be analyzed.

The interim analysis of Cohort A will also include sensitivity analyses for retrospective data changes made to seizure diary data: change from Baseline in seizure frequency, presented by Part 1 treatment and Part 2 mean daily dose, and percentage of subjects with improvement in seizure frequency from Baseline, for ESC-confirmed drop seizures, typical drop seizures, and individual seizure types. These sensitivity analysis will be completed using "Pre-DCR" seizure datasets provided by Signant Health.

Analyses will follow the plans spelled out elsewhere in this SAP. Other non-seizure related secondary endpoint data will not be included.

12.1.4 Exploratory Analyses

The sNDA interim analysis will include the following exploratory measures:

- The incidence of status epilepticus
- Incidence of rescue medication usage
- Number of days rescue medication used

Other exploratory endpoint data will not be included.

12.1.5 Descriptive Analyses

The sNDA interim analysis will include summaries of disposition, protocol deviations, study populations, demographic and baseline characteristics, and medications (concomitant, AEDs). These summaries will follow the plans specified elsewhere in this SAP for Part 2 as a whole.

12.1.6 Other Considerations

- Data handling rules will follow the conventions outlined in this SAP for Part 2 as a whole. This includes rule for imputing dates for AEs that may be missing date information at the time of the data snapshot.
- Since this is an open-label trial primarily focused on safety, there is no intent to stop the trial based on effectiveness results. No p-value adjustments will be made for this interim analysis.
- No individual subject's data will be considered fully locked at the time of the interim analysis since data can be corrected or augmented as subjects in Cohort A complete Part 2 and all data monitoring visits are completed. Cohort B will not be included in the interim analysis.
- An interim CSR will be prepared to summarize the results of the analysis.

12.2 Interim Analysis for Japanese Partial Change Application

12.2.1 Overview

An interim analysis of ZX008-1601 Part 2 Cohort B will be performed to support a Partial Change Application (PCA) to expand the indication for ZX008 in Japan to include the treatment of LGS. The interim analysis will be based on a snapshot of the clinical database taken on 09 September 2022 – a date chosen to ensure that the analysis includes at least 365 ± 4 days of exposure in Part 2 for all subjects in Cohort B. Like the sNDA interim analysis for Cohort A, this PCA interim analysis will comprise a large subset of the tables, listings and figures planned for the final analysis of Cohort B. A full list of the tables, listings and figures included in the interim analysis is given in Sections 17 and 18.

12.2.2 Safety Analyses

The primary purpose of the PCA interim analysis is the same as for Part 2: to assess the long-term safety and tolerability of ZX008 in children and adults with LGS. As such, the interim analysis will include all tables and listings that summarize AEs, laboratory assessments, vital signs, weight, BMI, physical and neurological exams, ECHO, ECG, C-SSRS data, IMP treatment exposure/dosage data, compliance with IMP intake, Tanner staging, and BRIEF questionnaire summaries. (Methods for the analysis of ECHO and ECG data are outside the scope of this SAP.)

12.2.3 Effectiveness Analyses

Since effectiveness measures are secondary objectives of this open-label extension, fewer effectiveness analyses will be included in this interim analysis than are specified for Part 2 as a whole. Specifically, the PCA interim analysis will focus on effectiveness measures related to the primary and key secondary seizure-related endpoints used to evaluate efficacy in the pivotal, Part 1 portion of the trial. These include analyses of:

- the frequency of seizures that result in drops (ESC-confirmed) and that do not result in drops,
- the proportion of subjects who attain 50% or greater decrease in seizures that result in drops (ESC-confirmed) and that do not result in drops, as well as a worsening or no change (i.e., ≤ 0% reduction), > 0%, ≥ 25%, ≥ 75%, 100% reduction, or near drop seizure freedom (i.e., 0 or 1 seizure) from Baseline
- the number of drop seizure-free days (ESC-confirmed)
- the longest interval between seizures that result in drops (ESC-confirmed)

Analyses of the effectiveness measure related to the non-seizure related Part 1 key secondary endpoint, the Clinical Global Impression – Improvement rating as assessed by the Principal Investigator, will also be performed for the OLE mITT Population overall and by age subgroups. The Clinical Global Impression – Improvement rating as assessed by the parent/caregiver will also be analyzed.

Analyses will follow the plans spelled out elsewhere in this SAP. Other non-seizure related secondary endpoint data will not be included.

12.2.4 Exploratory Analyses

The PCA interim analysis will include the following exploratory measures:

- The incidence of status epilepticus
- Incidence of rescue medication usage
- Number of days rescue medication used

Other exploratory endpoint data will not be included.

12.2.5 Descriptive Analyses

The PCA interim analysis will include summaries of disposition, protocol deviations, study populations, demographic and baseline characteristics, and medications (concomitant, AEDs).

12.2.6 Other Considerations

- Data handling rules will follow the conventions outlined in this SAP for Part 2 as a whole. This includes rule for imputing dates for AEs that may be missing date information at the time of the data snapshot.
- Since this is an open-label trial primarily focused on safety, there is no intent to stop the trial based on effectiveness results. No p-value adjustments will be made for this interim analysis.
- No individual subject's data will be considered fully locked at the time of the interim analysis since data can be corrected or augmented as subjects in Cohort B complete Part 2 and all data monitoring visits are completed. Cohort A will not be included in the PCA interim analysis.

An interim CSR will be prepared to summarize the results of the analysis.

12.3 Final Analyses for Cohort A and B

The final analysis of Part 2, Cohort A data will occur after all subjects in Cohort A have exited Part 2. The final analysis of Cohort B, Part 2 will be completed once those subjects have completed Part 2. Additional data cuts may be made for regulatory submissions.

13 Change from Planned Analyses

•Several changes specified to the secondary objectives of Part 2 in the protocol:

Protocol	SAP
–The change in the frequency of all countable motor seizures (GTC, TS, CS, AS, TA, FS, MS with a drop)	*Modified to:* The change in the frequency of all countable motor seizures (GTC, SGTC, TS, AS, TA, clonic seizures [CS], focal seizures with clear observable motor signs [FS], and hemiclonic seizures [HS])
	Added: Change in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) between baseline and the OLE Treatment Period whether ESC confirmed as drop or not.
	Added: The change in the frequency of all countable non-motor seizures (absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms)
The proportion of subjects who achieve a worsening or no change (i.e., ≤ 0% reduction), >0%, ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (i.e. 0 or 1 seizures) in frequency of all countable seizures that result in drops, countable motor seizures that do not result in drops, all countable motor seizures, all countable seizures, and all countable seizures that do not result in drops	*Modified to:* The proportion of subjects who have a worsening or no change (i.e., ≤ 0% reduction), >0 %, ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (i.e., 0 or 1 seizures) in frequency of all seizures that result in drops (ESC confirmed), typical drop seizures, all countable motor seizures, all countable non-motor seizures, and all countable seizures
Number of seizure-free days, defined as 1) days with no countable seizures and 2) days with no seizures that result in drops	*Modified to:* Number of seizure-free days, defined as 1) days with no seizures that results in drops (ESC confirmed), and 2) days with no countable motor seizures

•Several changes specified to the efficacy endpoints of Part 2 in the protocol:

Protocol	SAP
The change from baseline in the frequency of seizures that result in drops.	*Modified to:* The change from baseline in the frequency of seizures that result in drops (ESC-confirmed).

	Added: The change in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) between baseline and the OLE Treatment Period whether ESC confirmed as drop or not.
The change from baseline in the frequency of all countable motor seizures (GTC, TS, CS, AS, TA, FS, MS with a drop)	*Modified to:* The change from baseline in the frequency of all countable motor seizures (GTC, sGTC, TS, CS, AS, TA, FS, and HS)
	Added: The change in the frequency of all countable non-motor seizures (absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms)
The change from baseline in the frequency of all countable seizures	*Modified to:* The change from baseline in the frequency of all countable seizures (i.e., motor and non-motor)
The proportion of subjects who achieve a worsening or no change (i.e., ≤ 0% reduction), >0%, ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (i.e. 0 or 1 seizures) in frequency of all countable seizures that result in drops, countable motor seizures that do not result in drops, all countable motor seizures, all countable seizures, and all countable seizures that do not result in drops	*Modified to:* The proportion of subjects who have a worsening or no change (i.e., ≤ 0% reduction), >0 %, ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (i.e., 0 or 1 seizures) in frequency of all seizures that result in drops (ESC confirmed), typical drop seizures, all countable motor seizures, all countable non-motor seizures, and all countable seizures
Number of seizure-free days, defined as 1) days with no countable seizures and 2) days with no seizures that result in drops	*Modified to:* Number of seizure-free days, defined as 1) days with no seizures that results in drops (ESC confirmed), and 2) days with no countable motor seizures
Longest interval between seizures that result in drops	Longest interval between seizures that result in drops (ESC-confirmed)

- Due to COVID-19, many Cohort A subjects/caregivers in this trial delayed or missed their on-site study visits to mitigate hospital or clinic exposure to the most recently discovered coronavirus. Many sites have also delayed or missed onsite patient visits due to site closure, facility (e.g. ECHO) closure, and physician and/or coordinator availability. Though an interim analysis was not specified in the protocol, one is being conducted for Cohort A due to the unknowns associated with subjects unable or unwilling to attend their on-site visits, the increased risk of case resurgence/lockdown within various study site regions, and the uncertainty surrounding the

completion of EOS subject visits and the conduct of final monitoring visits. The interim analysis will be included in the next global protocol update should one be required prior to study closure.

- Analyses of all countable seizures that did not result in drops (i.e., Non-Drop seizures) were added to the SAP. The change from baseline in Non-Drop seizures and of the proportion of subjects who achieve a worsening from baseline (i.e., <= 0% reduction), or >0%, ≥ 25%, ≥ 50%, ≥ 75%, 100% reduction, and "near seizure freedom" (i.e., 0 or 1 seizures) from baseline in frequency of Non-Drop seizures were analyzed as specified for the other seizure groupings.
- A sensitivity analysis of SE events reported in the eDiary was conducted for a subset of SE seizure types officially recognized by the International League Against Epilepsy: GTC, SGTC, Focal with and without clear observable signs, absence/atypical absence. The SE events were presented in order of increasing emergency via the following groupings:
    - all SE episodes
    - SE episodes with no rescue medications administered
    - SE episodes with 1 rescue medication administered
    - SE episodes with > 1 rescue medication administered
- A pre-edited version of the seizure datasets for Cohort A was requested for regulatory submissions, intended to represent the original instance of data prior to modifications made as a result of cleaning for Part 1 Cohort A database lock. Upon sponsor request, Signant Health created 3 versions of pre-edited ("pre-DCR") datasets:
    - any edits made through the Trial Manager portal were removed,
    - any edits made through the Trial Manager portal or directly on the device itself were removed,
    - any edits made through the Trial Manager portal or directly on the device itself were removed, with the exception of the seizure classification field (this field is not subject-reported and is subject to review/query/approval by the Epilepsy Study Consortium).

  Sensitivity analyses for retrospective data changes, using the above 3 datasets, were performed. Analyses included the change from Baseline in seizure frequency and percentage of subjects with improvement in seizure frequency from Baseline for ESC-confirmed drop seizures, typical drop seizures, and individual seizure types.
- The planned analyses of the Vineland Adaptive Behavior Scale were not completed due to issues with the collection of the questionnaire on the eDiary device. The questionnaire was not administered in a way that allowed for determination of the domain scores. The requirement for administering this questionnaire was removed from the protocol in a protocol amendment and also removed from the SAP.
- Additional weight summary analyses by Part 1 Age group were added.

14 Programming Considerations

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

14.1 GENERAL CONSIDERATIONS

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

14.2 TABLE, LISTING, AND FIGURE FORMAT

14.2.1 General

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

14.2.2 Headers

- All output should have the following header at the top left of each page:

<Sponsor Name> Protocol XXX (Syneos Health study number xxx)

Draft/Final Run <date>

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

14.2.3 Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final determination (see also template 03.007C "Table of Contents for Tables Listings and Figures in Statistical Analysis Plan"). A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the

- Column headers. There will be 1 blank line between the last title and the solid line.

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

14.2.4 Column Headers

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

14.2.5 Body of the Data Display

General Conventions

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

Alphanumeric values are left-justified.

Numbers in table cells are center aligned.

Table Conventions

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

Severity Rating	N
severe	0
moderate	8
mild	3

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX

Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values should be output in the format: "0.xxxx", where xxxx is the value rounded to 4 decimal places. Any p-value less than 0.0001 will be presented as <0.0001. If the p-value is returned as >0.9999 then present as >0.9999
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% should be presented as 100%, without any decimal places.
- Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), medications (by preferred name), and adverse events (by preferred term) should be displayed. SOC terms are sorted alphabetically. Preferred terms are sorted in order of incidence within SOC terms. If incidence for more than 1 term is identical, they should then be sorted alphabetically.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

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

Listing Conventions

- Listings will be sorted for presentation in order of subject number, visit/collection day, and

visit/collection time.

- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

Figure Conventions

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

Footnotes

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

15 Reference List

ICH Topic E2F: Development Safety Update Report, 2011.

Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox–Gastaut syndrome. N Engl J Med. 2018;378:1888–97.

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Sparrow, S. S., & Cicchetti, D. V. (1989). The Vineland Adaptive Behavior Scales. In C. S. Newmark (Ed.), Major psychological assessment instruments, Vol. 2, pp. 199-231). Needham Heights, MA, US: Allyn & Bacon.

Talarska, D. (2007). The usefulness of Quality of Life Childhood Epilepsy (QOLCE) questionnaire in evaluating the quality of life of children with epilepsy. Advances in Medical Sciences, 52 Suppl 1, 191–193.

Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391:1085–96.

Tukey, JW (1977). Exploratory Data Analysis. Addison-Wesley.

Westphal-Guitti C, Alonso NB, Migliorini RCVP et al., "Quality of life and burden in caregivers of patients with epilepsy," The Journal of Neuroscience Nursing, vol. 39, no. 6, pp. 354–360, 2007.

16 Quality Control

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

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

17 Index of Tables and Figures

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
	14.1	**Demographic data and other baseline characteristics**		
	14.1.1	**Subject disposition**		
Table	14.1.1.1.3.1	Overall Subject Disposition in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population and OLE mITT Population	Y	N/A
Table	14.1.1.1.3.2	Overall Subject Disposition in Part 2 by Region (Cohort A - North America, Europe, Australia) - OLE Safety Population and OLE mITT Population	Y	N/A
Table	14.1.1.1.4	Overall Subject Disposition in Part 2 (Cohort B - Japan) - OLE Safety Population and OLE mITT Population	N/A	Y
Table	14.1.1.2.3	Major Protocol Deviations in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.1.2.4	Major Protocol Deviations in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.1.3.3	Study Populations in Part 2 (Cohort A - North America, Europe, Australia)	Y	N/A
Table	14.1.1.3.4	Study Populations in Part 2 (Cohort B - Japan)	N/A	Y
Table	14.1.1.4.1	Part 2 Subject Visits Missed or not Conducted in Person due to COVID-19 (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.1.1.4.2	Part 2 Subject Visits Missed or not Conducted in Person due to COVID-19 (Cohort B - Japan) - OLE Safety Population	N/A	Y
	14.1.2	**Demographic and other Baseline Characteristics**		
Table	14.1.2.1.3	Demographic and Baseline Characteristics in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.2.1.4	Demographic and Baseline Characteristics in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.2.1.5	Demographic and Baseline Characteristics in Part 2 by Geographic Region (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.2.2.3	Demographic and Baseline Characteristics in Part 2 (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.1.2.2.4	Demographic and Baseline Characteristics in Part 2 (Cohort B - Japan) - OLE mITT Population	N/A	Y
	14.1.4	**Prior and concomitant medication/treatment**		
Table	14.1.4.2.3	Concomitant Medications and Therapies/Treatments in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.1.4.2.4	Concomitant Medications and Therapies/Treatments in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.4.4.1.3	Concomitant Antiepileptic Treatment in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.4.4.1.4	Concomitant Antiepileptic Treatment in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.4.4.2.3	Rescue Medications in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	N	N/A
Table	14.1.4.4.2.4	Rescue Medications in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	N
	14.1.5	**Treatment Exposure and compliance**		
Table	14.1.5.1.3	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.4	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.1.5.1	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) and Part 1 Age Subgroup (Cohort A - North America,	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Europe, Australia) - OLE Safety Population		
Table	14.1.5.1.5.2	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) and Sex (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.5.3	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) and Weight Subgroup (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.5.4	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) and Number of Concomitant Antiepileptic Medications Subgroup (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.6.1	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) and Part 1 Age Subgroup (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.1.6.2	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) and Sex (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.1.6.3	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) and Weight Subgroup (Cohort B - Japan) - OLE Safety Population	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.1.5.1.6.4	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/kg/day) and Number of Concomitant Antiepileptic Medications Subgroup (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.1.7.1	Number of Subjects Receiving ZX008 in Part 2 According to Mean Daily Dose (mg/kg/day) and Duration of Treatment (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.7.2	Number of Subjects Receiving ZX008 in Part 2 According to Mean Daily Dose (mg/kg/day) and Duration of Treatment (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.1.8.1	Duration of ZX008 Treatment Exposure by Dose Level During Part 1 Through Part 2 by Mean Daily Dose (mg/kg/day) (Cohort A - North America, Europe, Australia) - LT SAF Population	Y	N/A
Table	14.1.5.1.8.2	Duration of ZX008 Treatment Exposure by Dose Level During Part 1 Through Part 2 by Mean Daily Dose (mg/kg/day) (Cohort B - Japan) - LT SAF Population	N/A	Y
Table	14.1.5.1.9.1	Number of Subjects Receiving ZX008 According to Mean Daily Dose and Duration of Treatment During Part 1 Through Part 2 (Cohort A - North America, Europe, Australia) - LT SAF Population	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.1.5.1.9.2	Number of Subjects Receiving ZX008 According to Mean Daily Dose and Duration of Treatment During Part 1 Through Part 2 (Cohort B -Japan) - LT SAF Population	N/A	Y
Table	14.1.5.1.9.3	Number of Subjects Receiving ZX008 According to Mean Daily Dose (mg/day) and Duration of Treatment During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.9.4	Number of Subjects Receiving ZX008 According to Mean Daily Dose (mg/day) and Duration of Treatment During Part 2 (Cohort B -Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.1.10.1	Duration of ZX008 Treatment According to Assigned Dosage During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.10.2	Duration of ZX008 Treatment According to Assigned Dosage During Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.1.11.1	Shift in ZX008 Dosage Received in Part 2 by Study Visit (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.11.2	Shift in ZX008 Dosage Received in Part 2 by Study Visit (Cohort B - Japan) - OLE Safety Population	N	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.1.5.1.12.1.1	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/day) in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.12.1.2	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/day) in Part 2 by Part 1 Age Subgroup (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.12.1.3	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/day) in Part 2 by Weight Subgroup (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.1.12.2.1	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/day) in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.1.12.2.2	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/day) in Part 2 by Part 1 Age Subgroup (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.1.12.2.3	Duration of IMP Treatment Exposure in Part 2 by Mean Daily Dose (mg/day) in Part 2 by Weight Subgroup (Cohort B - Japan) - OLE Safety Population	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.1.5.2.1.3.1	Compliance to IMP Intake in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.1.5.2.1.3.2	Compliance to IMP Intake in Part 2 (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.1.5.2.1.3.3	Compliance to IMP Intake in Part 1 Through Part 2 (Cohort A - North America, Europe, Australia) - Safety Population for Part 1	Y	N/A
Table	14.1.5.2.1.4.1	Compliance to IMP Intake in Part 2 Based on Subject Diary (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.2.1.4.2	Compliance to IMP Intake in Part 2 Based on Subject Diary (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.1.5.2.1.4.3	Compliance to IMP Intake in Part 1 Through Part 2 Based on Subject Diary (Cohort B - Japan) - Safety Population for Part 1	N/A	Y
Table	14.1.5.2.3.3.1	Compliance to IMP Intake in Part 2 Based on Bottle Weight (Cohort A - North America, Europe, Australia) - OLE Safety Population	N	N/A
Table	14.1.5.2.3.3.2	Compliance to IMP Intake in Part 2 Based on Bottle Weight (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.1.5.2.3.3.3	Compliance to IMP Intake in Part 1 Through Part 2 based on Bottle Weight (Cohort A - North America,	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Europe, Australia) -Safety Population for Part 1		
Table	14.1.5.2.3.4.1	Compliance to IMP Intake in Part 2 based on Bottle Weight (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.1.5.2.3.4.2	Compliance to IMP Intake in Part 2 based on Bottle Weight (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.1.5.2.3.4.3	Compliance to IMP Intake in Part 1 Through Part 2 based on Bottle Weight (Cohort B - Japan) - Safety Population for Part 1	N/A	Y
	14.2	**Efficacy**		
	14.2.1	**Seizures resulting in drops (ESC Confirmed)**		
Table	14.2.1.11.1.1.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.1.11.1.1.1a	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1) - OLE mITT Population	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.2.1.11.1.1.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - OLE mITT Population	Y	N/A
Table	14.2.1.11.1.1.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - OLE mITT Population	Y	N/A
Table	14.2.1.11.1.1.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.1.11.1.1.2a	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1) - OLE mITT Population	Y	N/A
Table	14.2.1.11.1.1.2b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - OLE mITT Population		
Table	14.2.1.11.1.1.2c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - OLE mITT Population	Y	N/A
Table	14.2.1.11.1.1.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Age Group: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.1.11.1.1.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Part 1 Baseline Weight Subgroup: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.1.11.1.1.5	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Sex: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America,	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Europe, Australia) - OLE mITT Population		
Table	14.2.1.11.1.1.6	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Geographic Region: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.1.11.1.1.7	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Number of Prior Antiepileptic Treatments Used: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.1.11.1.1.8	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Number of Concomitant Antiepileptic Treatments Used: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.1.11.1.1.9	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Baseline Frequency of Seizures Resulting in Drops: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Figure	14.2.1.11.1.1.10	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Treatment Received during Part 1: Observed Medians (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.1.11.1.2.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Treatment Received during Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.1.11.1.2.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2. 1.11.1.2.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Age Group: Summary Statistics and Tests of Changes from Baseline (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2. 1.11.1.2.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 by Part 1 Baseline Weight Subgroup: Summary Statistics and Tests of Changes from Baseline (Cohort B - Japan) - OLE mITT Population	N/A	Y
Figure	14.2.1.11.1.2.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		During Part 2 by Treatment Received During Part 1: Observed Medians (Cohort B - Japan) - OLE mITT Population		
Table	14.2.1.12.1.1.1	Percent Reduction in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 (Cohort A - Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.1.12.1.1.1a	Percent Reduction in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1) - OLE mITT Population	Y	N/A
Table	14.2.1.12.1.1.1b	Percent Reduction in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - OLE mITT Population	Y	N/A
Table	14.2.1.12.1.1.1c	Percent Reduction in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - OLE mITT Population	Y	N/A
Table	14.2.1.12.1.2.1	Percent Reduction in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days During Part 2	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		(Cohort B - Japan) - OLE mITT Population		
Figure	14.2.1.13.1.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Figure	14.2.1.13.1.1.1a	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1)- OLE mITT Population	Y	N/A
Figure	14.2.1.13.1.1.1b	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2)- OLE mITT Population	Y	N/A
Figure	14.2.1.13.1.1.1c	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Dataset Version 3)- OLE mITT Population		
Figure	14.2.1.13.1.2.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) During Part 2 Treatment Period (Cohort B - Japan) - OLE mITT Population	N/A	Y
	14.2.2	**Efficacy - Clinical Global Impression - Improvement rating by Investigator**		
Table	14.2.2.4.1.1	Clinical Global Impression - Improvement Rating by Investigator in Part 2 by Treatment Received in Part 1 (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.2.4.1.2	Clinical Global Impression - Improvement Rating by Investigator in Part 2 by Treatment Received in Part 1 (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.2.4.2.1	Clinical Global Impression - Improvement Rating by Investigator in Part 2 by Part 1 Age Subgroup (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.2.4.2.2	Clinical Global Impression - Improvement Rating by Investigator in Part 2 by Sex (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.2.2.4.2.3	Clinical Global Impression - Improvement Rating by Investigator in Part 2 by Part 1 Weight Subgroup (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.2.4.2.4	Clinical Global Impression - Improvement Rating by Investigator in Part 2 Number of Concomitant Antiepileptic Medications Used (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.2.4.2.5	Clinical Global Impression - Improvement Rating by Investigator in Part 2 by Part 1 Age Subgroup (Cohort B - Japan) - OLE mITT Population	N/A	Y
Figure	14.2.2.4.3.1	Distribution of Clinical Global Impression - Improvement Rating by Investigator at Last Assessment in Part 2 (Cohort A - North America, Europe, Australia)- OLE mITT Population	Y	N/A
Figure	14.2.2.4.3.2	Distribution of Clinical Global Impression - Improvement Rating by Investigator at Last Assessment in Part 2 (Cohort B - Japan) OLE mITT Population	N/A	Y
	14.2.3	**Countable Motor Seizures**		
Table	14.2.3.6.1.1.1	Frequency of Countable Motor Seizures per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A -	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		North America, Europe, Australia) - OLE mITT Population		
Table	14.2.3.6.1.1.2	Frequency Countable Motor Seizures per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.3.6.1.1.3	Frequency of Countable Motor Seizures per 28 days During Part 2 by Part 1 Age Group: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.3.6.1.1.4	Frequency of Countable Motor Seizures per 28 days During Part 2 by Part 1 Baseline Weight Subgroup: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.3.6.1.1.5	Frequency of Countable Motor Seizures per 28 days During Part 2 by Sex: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.3.6.1.1.6	Frequency of Countable Motor Seizures per 28 days During Part 2 by Geographic Region: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.2.3.6.1.1.7	Frequency of Countable Motor Seizures per 28 days During Part 2 by Number of Prior Antiepileptic Treatments Used: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.3.6.1.1.8	Frequency of Countable Motor Seizures per 28 days During Part 2 by Number of Concomitant Antiepileptic Treatments Used: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.3.6.1.1.9	Frequency of Countable Motor Seizures per 28 days During Part 2 by Baseline Frequency of Seizures Resulting in Drops: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Figure	14.2.3.6.1.1.10	Frequency of Countable Motor Seizures per 28 days During Part 2 by Treatment Received during Part 1: Observed Medians (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.3.6.1.2.1	Frequency of Countable Motor Seizures per 28 days During Part 2 by Treatment Received during Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort B - Japan) - OLE mITT Population	N/A	N

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.2.3.6.1.2.2	Frequency of Countable Motor Seizures per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort B - Japan) - OLE mITT Population	N/A	N
Figure	14.2.3.6.1.2.3	Frequency of Countable Motor Seizures per 28 days During Part 2 by Treatment Received during Part 1: Observed Medians (Cohort B - Japan) - OLE mITT Population	N/A	N
Table	14.2.3.7.1.1.1	Percent Reduction in Frequency of Countable Motor Seizures per 28 days During Part 2 (Cohort A - Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.3.7.1.2.1	Percent Reduction in Frequency of Countable Motor Seizures per 28 days During Part 2 (Cohort B - Japan) - OLE mITT Population	N/A	N
Figure	14.2.3.8.1.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Countable Motor Seizures During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Figure	14.2.3.8.1.2.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Countable Motor Seizures During Part 2 Treatment Period (Cohort B - Japan) - OLE mITT Population	N/A	N

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
	14.2.4.1	**Efficacy - Typical Drop Seizures**		
Table	14.2.4.1.6.1.1.1	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.4.1.6.1.1.1a	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1)- OLE mITT Population	Y	N/A
Table	14.2.4.1.6.1.1.1b	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - OLE mITT Population	Y	N/A
Table	14.2.4.1.6.1.1.1c	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - OLE mITT Population	Y	N/A
Table	14.2.4.1.6.1.1.2	Frequency Seizures that Typically Result in Drops per 28 days During	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population		
Table	14.2.4.1.6.1.1.2a	Frequency Seizures that Typically Result in Drops per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1) - OLE mITT Population	Y	N/A
Table	14.2.4.1.6.1.1.2b	Frequency Seizures that Typically Result in Drops per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - OLE mITT Population	Y	N/A
Table	14.2.4.1.6.1.1.2c	Frequency Seizures that Typically Result in Drops per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - OLE mITT Population	Y	N/A
Table	14.2.4.1.6.1.1.3	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Part 1 Age Group: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America,	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Europe, Australia) - OLE mITT Population		
Table	14.2.4.1.6.1.1.4	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Part 1 Baseline Weight Subgroup: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.1.6.1.1.5	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Sex: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.1.6.1.1.6	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Geographic Region: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.1.6.1.1.7	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Number of Prior Antiepileptic Treatments Used: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.1.6.1.1.8	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Number of Concomitant Antiepileptic Treatments Used:	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population		
Table	14.2.4.1.6.1.1.9	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Baseline Frequency of Seizures Resulting in Drops: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Figure	14.2.4.1.6.1.1.10	Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 by Treatment Received During Part 1: Observed Medians (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.4.1.6.1.2.1	Frequency of Seizures That Typically Result in Drops per 28 Days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes From Baseline (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.4.1.6.1.2.2	Frequency of Seizures That Typically Result in Drops per 28 Days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes From Baseline (Cohort B - Japan) - OLE mITT Population	N/A	Y
Figure	14.2.4.1.6.1.2.3	Frequency of Seizures That Typically Result in Drops per 28 Days During Part 2 by Treatment Received During	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Part 1: Observed Medians (Cohort B - Japan) - OLE mITT Population		
Table	14.2.4.1.7.1.1.1	Percent Reduction in Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 (Cohort A - Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.4.1.7.1.1.1a	Percent Reduction in Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1) - OLE mITT Population	Y	N/A
Table	14.2.4.1.7.1.1.1b	Percent Reduction in Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - OLE mITT Population	Y	N/A
Table	14.2.4.1.7.1.1.1c	Percent Reduction in Frequency of Seizures that Typically Result in Drops per 28 days During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - OLE mITT Population	Y	N/A
Table	14.2.4.1.7.1.2.1	Percent Reduction in Frequency of Seizures That Typically Result in Drops per 28 Days During Part 2 (Cohort B - Japan) - OLE mITT Population	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Figure	14.2.4.1.8.1.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures that Typically Result in Drops During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Figure	14.2.4.1.8.1.1.1a	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures that Typically Result in Drops During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1) - OLE mITT Population	Y	N/A
Figure	14.2.4.1.8.1.1.1b	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures that Typically Result in Drops During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - OLE mITT Population	Y	N/A
Figure	14.2.4.1.8.1.1.1c	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures that Typically Result in Drops During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3)- OLE mITT Population	Y	N/A
Figure	14.2.4.1.8.1.2.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures That Typically Result in Drops During Part	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		2 Treatment Period (Cohort B - Japan) - OLE mITT Population		
	14.2.4.2	**Efficacy - Countable Non-Motor Seizures**		
Table	14.2.4.2.6.1.1.1	Frequency of Countable Non-Motor Seizures per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.2.6.1.1.2	Frequency Countable Non-Motor Seizures per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.2.6.1.1.3	Frequency of Countable Non-Motor Seizures per 28 days During Part 2 by Age Group: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.2.6.1.1.4	Frequency of Countable Non-Motor Seizures per 28 days During Part 2 by Part 1 Baseline Weight Subgroup: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.2.6.1.1.5	Frequency of Countable Non-Motor Seizures per 28 days During Part 2 by Sex: Summary Statistics and Tests of	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population		
Table	14.2.4.2.6.1.1.6	Frequency of Countable Non-Motor Seizures per 28 days During Part 2 by Geographic Region: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.2.6.1.1.7	Frequency of Countable Non-Motor Seizures per 28 days During Part 2 by Number of Prior Antiepileptic Treatments Used: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.2.6.1.1.8	Frequency of Countable Non-Motor Seizures per 28 days During Part 2 by Number of Concomitant Antiepileptic Treatments Used: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.2.6.1.1.9	Frequency of Countable Non-Motor Seizures per 28 days During Part 2 by Baseline Frequency of Seizures Resulting in Drops: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Figure	14.2.4.2.6.1.1.10	Frequency of Countable Non-Motor Seizures per 28 days During Part 2 by	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Treatment Received During Part 1: Observed Medians (Cohort A - North America, Europe, Australia) - OLE mITT Population		
Table	14.2.4.2.6.1.2.1	Frequency of Countable Non-Motor Seizures per 28 Days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes From Baseline (Cohort B - Japan) - OLE mITT Population	N/A	N
Table	14.2.4.2.6.1.2.2	Frequency of Countable Non-Motor Seizures per 28 Days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes From Baseline (Cohort B - Japan) - OLE mITT Population	N/A	N
Figure	14.2.4.2.6.1.2.3	Frequency of Countable Non-Motor Seizures per 28 Days During Part 2 by Treatment Received During Part 1: Observed Medians (Cohort B - Japan) - OLE mITT Population	N/A	N
Table	14.2.4.2.7.1.1.1	Percent Reduction in Frequency of Countable Non-Motor Seizures per 28 days During Part 2 (Cohort A - Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.2.7.1.2.1	Percent Reduction in Frequency of Countable Non-Motor Seizures per 28 Days During Part 2 (Cohort B - Japan) - OLE mITT Population	N/A	N
Figure	14.2.4.2.8.1.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Countable Non-Motor Seizures During Part 2	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Treatment Period (Cohort A - North America, Europe, Australia) - OLE mITT Population		
Figure	14.2.4.2.8.1.2.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Countable Non-Motor Seizures During Part 2 Treatment Period (Cohort B - Japan) - OLE mITT Population	N/A	N
	14.2.4.3	**Efficacy - All Countable Seizures (Motor + Non-Motor)**		
Table	14.2.4.3.6.1.1.1	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.3.6.1.1.2	Frequency All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.3.6.1.1.3	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 by Part 1 Age Group: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.3.6.1.1.4	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		During Part 2 by Part 1 Baseline Weight Subgroup: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population		
Table	14.2.4.3.6.1.1.5	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 by Sex: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.3.6.1.1.6	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 by Geographic Region: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.3.6.1.1.7	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 by Number of Prior Antiepileptic Treatments Used: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.3.6.1.1.8	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 by Number of Concomitant Antiepileptic Treatments Used: Summary Statistics and Tests of Changes from Baseline	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		(Cohort A - North America, Europe, Australia) - OLE mITT Population		
Table	14.2.4.3.6.1.1.9	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 by Baseline Frequency of Seizures Resulting in Drops: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Figure	14.2.4.3.6.1.1.10	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 by Treatment Received During Part 1: Observed Medians (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.3.6.1.2.1	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 Days During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes From Baseline (Cohort B - Japan) - OLE mITT Population	N/A	N
Table	14.2.4.3.6.1.2.2	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 Days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics and Tests of Changes From Baseline (Cohort B - Japan) - OLE mITT Population	N/A	N
Figure	14.2.4.3.6.1.2.3	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 Days During Part 2 by Treatment Received During Part 1: Observed Medians	N/A	N

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		(Cohort B - Japan) - OLE mITT Population		
Table	14.2.4.3.7.1.1.1	Percent Reduction in Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days During Part 2 (Cohort A - Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.4.3.7.1.2.1	Percent Reduction in Frequency of All Countable Seizures (Motor + Non-Motor) per 28 Days During Part 2 (Cohort B - Japan) - OLE mITT Population	N/A	N
Figure	14.2.4.3.8.1.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in All Countable Seizures (Motor + Non-Motor) During Part 2 Treatment Period (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Figure	14.2.4.3.8.1.2.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in All Countable Seizures (Motor + Non-Motor) During Part 2 Treatment Period (Cohort B - Japan) - OLE mITT Population	N/A	N
	14.2.4.5	**Efficacy - All Countable Seizures that did not Result in Drops (ESC Confirmed)**		
Table	14.2.4.5.6.1.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population		
Table	14.2.4.5.6.1.2	Frequency of All Countable Seizures That did not Result in Drops (ESC Confirmed) During Part 2 by Treatment Received During Part 1: Summary Statistics and Tests of Changes From Baseline (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.4.5.6.1.3	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) During Part 2 by Part 1 Age Group: Summary Statistics and Tests of Changes from Baseline (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.4.5.6.1.4	Frequency of All Countable Seizures That did not Result in Drops (ESC Confirmed) During Part 2 by Part 1 Age Group: Summary Statistics and Tests of Changes From Baseline (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.4.5.7.1.1	Percent Reduction in Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) During Part 2 (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.4.5.7.1.2	Percent Reduction in Frequency of All Countable Seizures That did not Result in Drops (ESC Confirmed)	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		During Part 2 (Cohort B - Japan) - OLE mITT Population		
	14.2.5	**Efficacy - Seizure-free Days**		
Table	14.2.5.3.1	Number of Drop Seizure-Free Days per 28 Days (ESC Confirmed) During Part 2: Summary Statistics and Tests of Changes from Baseline by Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.5.3.2	Number of Drop Seizure-Free Days per 28 Days (ESC Confirmed) During Part 2: Summary Statistics and Tests of Changes From Baseline by Part 2 Mean Daily Dose (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.5.4.1	Number of Seizures that Typically Result in Drops Seizure-Free Days per 28 Days During Part 2: Summary Statistics and Tests of Changes from Baseline by Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.5.4.2	Number of Seizures that Typically Result in Drops Seizure-Free Days per 28 Days During Part 2: Summary Statistics and Tests of Changes From Baseline by Part 2 Mean Daily Dose (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.5.5.1	Number of Countable Motor Seizure-Free Days per 28 Days During Part 2: Summary Statistics and Tests of Changes from Baseline by Part 2	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE mITT Population		
Table	14.2.5.5.2	Number of Countable Motor Seizure-Free Days per 28 Days During Part 2: Summary Statistics and Tests of Changes From Baseline by Part 2 Mean Daily Dose (Cohort B - Japan) - OLE mITT Population	N	Y
	14.2.6	**Efficacy - Duration of the Longest Interval Between Seizures**		
Table	14.2.6.5.1	Duration of Longest Interval Between Seizures Resulting in Drops (ESC Confirmed) During Part 2 (Cohort A - North America, Europe, Australia)- OLE mITT Population	Y	N/A
Table	14.2.6.5.2	Duration of Longest Interval Between Seizures Resulting in Drops (ESC Confirmed) During Part 2 (Cohort B - Japan)- OLE mITT Population	N/A	Y
Figure	14.2.6.5.3	Boxplot of the Duration of Longest Interval Between Seizures Resulting in Drops (ESC Confirmed) During Part 2 (Cohort A - North America, Europe, Australia)- OLE mITT Population	Y	N/A
Figure	14.2.6.5.4	Boxplot of the Duration of Longest Interval Between Seizures Resulting in Drops (ESC Confirmed) During Part 2 (Cohort B - Japan)- OLE mITT Population	N/A	Y
Table	14.2.6.6.1	Duration of Longest Interval Between Seizures that Typically Result in Drops During Part 2 (Cohort A - North	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		America, Europe, Australia)- OLE mITT Population		
Table	14.2.6.6.2	Duration of Longest Interval Between Seizures That Typically Result in Drops During Part 2 (Cohort B - Japan)- OLE mITT Population	N/A	Y
Figure	14.2.6.6.3	Boxplot of the Duration of Longest Interval Between Seizures that Typically Result in Drops During Part 2 (Cohort A - North America, Europe, Australia)- OLE mITT Population	Y	N/A
Figure	14.2.6.6.4	Boxplot of the Duration of Longest Interval Between Seizures That Typically Result in Drops During Part 2 (Cohort B - Japan)- OLE mITT Population	N/A	Y
Table	14.2.6.7.1	Duration of Longest Interval Between Countable Motor Seizures During Part 2 (Cohort A - North America, Europe, Australia)- OLE mITT Population	N	N/A
Table	14.2.6.7.2	Duration of Longest Interval Between Countable Motor Seizures During Part 2 (Cohort B - Japan) - OLE mITT Population	N/A	N
Figure	14.2.6.7.3	Boxplot of the Duration of Longest Interval Between Countable Motor Seizures During Part 2 (Cohort A - North America, Europe, Australia)- OLE mITT Population	N	N/A
Figure	14.2.6.7.4	Boxplot of the Duration of Longest Interval Between Countable Motor	N/A	N

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Seizures During Part 2 (Cohort B - Japan)- OLE mITT Population		
	14.2.7	**Efficacy - Clinical Global Impression - Improvement rating by Parent/Caregiver**		
Table	14.2.7.3.1.1	Clinical Global Impression - Improvement Rating by Parent/Caregiver in Part 2 by Treatment Received in Part 1 (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.7.3.1.2	Clinical Global Impression - Improvement Rating by Parent/Caregiver in Part 2 by Treatment Received in Part 1 (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.7.3.2.1	Clinical Global Impression - Improvement Rating by Parent/Caregiver in Part 2 by Part 1 Age Subgroup (Cohort A - North America, Europe, Australia) - mITT Population	Y	N/A
Table	14.2.7.3.2.2	Clinical Global Impression - Improvement Rating by Parent/Caregiver in Part 2 by Sex (Cohort A - North America, Europe, Australia) - mITT Population	N	N/A
Table	14.2.7.3.2.3	Clinical Global Impression - Improvement Rating by Parent/Caregiver in Part 2 by Part 1 Weight Subgroup (Cohort A - North America, Europe, Australia) - mITT Population	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.2.7.3.2.4	Clinical Global Impression - Improvement Rating by Parent/Caregiver in Part 2 by Number of Concomitant Antiepileptic Medications Used (Cohort A - North America, Europe, Australia) - mITT Population	N	N/A
Table	14.2.7.3.2.5	Clinical Global Impression - Improvement Rating by Parent/Caregiver in Part 2 by Part 1 Age Subgroup (Cohort B - Japan) - mITT Population	N/A	Y
Figure	14.2.7.3.3.1	Distribution of Clinical Global Impression - Improvement Rating by Parent/Caregiver at Last Assessment in Part 2 (Cohort A - North America, Europe, Australia)- mITT Population	Y	N/A
Figure	14.2.7.3.3.2	Distribution of Clinical Global Impression - Improvement Rating by Parent/Caregiver at Last Assessment in Part 2 (Cohort B - Japan) - mITT Population	N/A	Y
	14.2.8	**Efficacy - Incidence of Status Epilepticus**		
Table	14.2.8.3.1.1	Number of Episodes of Status Epilepticus (SE) per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.8.3.1.2	Number of Episodes of Status Epilepticus (SE) per 28 days During Part 2 by Part 1 Age Group: Summary Statistics (Cohort A - North America,	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Europe, Australia) - OLE mITT Population		
Table	14.2.8.3.1.3	Number of Episodes of Status Epilepticus (SE) per 28 days During Part 2 by Sex: Summary Statistics (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.8.3.1.4	Number of Episodes of Status Epilepticus (SE) per 28 days During Part 2 by Geographic Region: Summary Statistics (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.8.3.2	Number of Episodes of Status Epilepticus (SE) per 28 Days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.8.4.1	Sensitivity Analysis for Number of Episodes of Status Epilepticus (SE) per 28 days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.8.4.2	Sensitivity Analysis for Number of Episodes of Status Epilepticus (SE) per 28 Days During Part 2 by Part 2 Mean Daily Dose: Summary Statistics (Cohort B - Japan) - OLE mITT Population	N/A	Y
	14.2.9	**Efficacy - Rescue Medication**		
Table	14.2.9.4.1	Days with Rescue Medication Usage in Part 2 by Part 2 Mean Daily Dose	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		(Cohort A - North America, Europe, Australia) - OLE mITT Population		
Table	14.2.9.4.2	Days With Rescue Medication Usage in Part 2 by Part 2 Mean Daily Dose (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.9.5.1	Number of Rescue Medications Used per Status Epilepticus Episode in Part 2 by Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.9.5.2	Number of Rescue Medications Used per Status Epilepticus Episode in Part 2 by Part 2 Mean Daily Dose (Cohort B - Japan) - OLE mITT Population	N/A	Y
Table	14.2.9.6.1	Categorical Analysis of Change from Baseline in the Number of Days with Rescue Medication Usage in Part 2 by Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE mITT Population	Y	N/A
Table	14.2.9.6.2	Categorical Analysis of Change From Baseline in the Number of Days With Rescue Medication Usage in Part 2 by Part 2 Mean Daily Dose (Cohort B - Japan) - OLE mITT Population	N/A	Y
	14.2.10	**Efficacy - Hospitalization and Resource Utilization for Treatment of Seizures**		
Table	14.2.10.2.1	Hospitalization and Other Healthcare Resource Utilization During the Study: Summary Statistics (Cohort A -	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		North America, Europe, Australia) - OLE mITT Population		
Table	14.2.10.2.2	Hospitalization and Other Healthcare Resource Utilization During the Study: Summary Statistics (Cohort B - Japan) - OLE mITT Population	N/A	N
	14.2.12	**Exploratory Efficacy - Quality of Life in Childhood Epilepsy Scale**		
Table	14.2.12.2.1	Quality of Life in Childhood Epilepsy (QOLCE) in Part 2 by Treatment Received During Part 1: Summary Statistics (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.12.2.2	Quality of Life in Childhood Epilepsy (QOLCE) in Part 1 by Treatment Received During Part 1: Summary Statistics (Cohort B - Japan) - OLE mITT Population	N/A	N
	14.2.13	**Exploratory Efficacy - Zarit Caregiver Burden Inventory**		
Table	14.2.13.3.1	Zarit Caregiver Burden Inventory During Part 2 by Treatment Received During Part 1: Amount of Burden Categories (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.13.3.2	Zarit Caregiver Burden Inventory During 2 by Treatment Received During Part 1: Amount of Burden Categories (Cohort B - Japan) - OLE mITT Population	N/A	N

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.2.13.4.1	Zarit Caregiver Inventory Index Score During Part 2 by Treatment Received During Part 1: Summary Statistics (Cohort A - North America, Europe, Australia)- OLE mITT Population	N	N/A
Table	14.2.13.4.2	Zarit Caregiver Inventory Index Score During Part 2 by Treatment Received During Part 1: Summary Statistics (Cohort B - Japan)- OLE mITT Population	N/A	N
	14.2.14	**Exploratory Efficacy - Parent /Caregiver Ratings using HADS Scale**		
Table	14.2.14.3.1	Parent/Caregiver Ratings Based on Hospital Anxiety and Depression Scale (HADS) During Part 2 by Treatment Received During Part 1: Normal; Borderline Abnormal, and Abnormal Categories (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A
Table	14.2.14.3.2	Parent/Caregiver Ratings Based on Hospital Anxiety and Depression Scale (HADS) During Part 2 by Treatment Received During Part 1: Normal; Borderline Abnormal, and Abnormal Categories (Cohort B - Japan) - OLE mITT Population	N/A	N
Table	14.2.14.4.1	Parent/Caregiver Ratings Based on Hospital Anxiety and Depression Scale (HADS) During Part 2 by Treatment Received During Part 1: Summary Descriptive Statistics (Cohort A - North America, Europe, Australia) - OLE mITT Population	N	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.2.14.4.2	Parent/Caregiver Ratings Based on Hospital Anxiety and Depression Scale (HADS) During Part 2 by Treatment Received During Part 1: Summary Descriptive Statistics (Cohort B - Japan) - OLE mITT Population	N/A	N
	14.2.15	**Exploratory Efficacy - Assessment of Seizure Burden After OLE Month 12 (Cohort B - Japan)**		
Table	**14.2.15.1**	Investigator's Assessment of Seizure Burden After OLE Month 12 by Treatment Received During Part 1 (Cohort B - Japan) - OLE mITT Population	**N/A**	**N**
	14.3	**Safety**		
	14.3.1	**Summary of adverse events**		
Table	14.3.1.1.1.3.1	Overview of Number of Subjects with TEAE During Part 2 by Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.1.1.3.2	Overview of Number of Subjects with TEAE During Part 2 by Part 2 Modal Dose (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.1.1.3.3	Overview of Number of Subjects with TEAE During Part 2 by Dosage at Onset (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.3.1.1.1.4.1	Overview of Number of Subjects With TEAE During Part 2 by Part 2 Mean Daily Dose (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.1.1.4.2	Overview of Number of Subjects With TEAE During Part 2 by Part 2 Modal Dose (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.1.1.4.3	Overview of Number of Subjects With TEAE During Part 2 by Dosage at Onset (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.2.1.3.1.1	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.2.1.3.1.2	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.2.1.3.1.3	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.2.1.3.1.4	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects in Part 2 by MedDRA System Organ Class, Preferred Term, and	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE Safety Population		
Table	14.3.1.2.1.3.1.5	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.2.1.3.1.6	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.2.1.3.2.1	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.2.1.3.2.2	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.2.1.3.2.3	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.2.1.3.2.4	Treatment-Emergent Adverse Events that Occurred in at Least 10% of	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Subjects in Any Dosage Group or Overall in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort B - Japan)- OLE Safety Population		
Table	14.3.1.2.1.3.2.5	Treatment-Emergent Adverse Events That Occurred in at Least 10% of Subjects in Any Dosage Group or Overall in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.2.1.3.2.6	Treatment-Emergent Adverse Events That Occurred in at Least 10% of Subjects in Any Dosage Group or Overall in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.2.2.3	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, Dosage at Onset, and Part 1 Age Group (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.2.2.4	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, Dosage at Onset, and Part 1 Age Group (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.2.3.3	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, Dosage at Onset, and Sex (Cohort A - North	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		America, Europe, Australia)- OLE Safety Population		
Table	14.3.1.2.3.4	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, Dosage at Onset, and Sex (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.2.4.3	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, and Usage of Most Commonly Used Antiepileptic Medications (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.2.4.4	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, and Usage of Most Commonly Used Antiepileptic Medications (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.3.1.3.1	TEAEs Leading to Study Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.3.1.3.2	TEAEs Leading to Study Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.3.1.3.3	TEAEs Leading to Study Discontinuation in Part 2 by MedDRA	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		System Organ Class, Preferred Term, and Dosage at Onset (Cohort A - North America, Europe, Australia)- OLE Safety Population		
Table	14.3.1.3.1.3.4	TEAEs Leading to Treatment Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.3.1.3.5	TEAEs Leading to Treatment Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.3.1.3.6	TEAEs Leading to Treatment Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.3.1.4.1	TEAEs Leading to Study Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.3.1.4.2	TEAEs Leading to Study Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.3.1.4.3	TEAEs Leading to Study Discontinuation in Part 2 by MedDRA	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		System Organ Class, Preferred Term, and Dosage at Onset (Cohort B - Japan)- OLE Safety Population		
Table	14.3.1.3.1.4.4	TEAEs Leading to Treatment Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.3.1.4.5	TEAEs Leading to Treatment Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.3.1.4.6	TEAEs Leading to Treatment Discontinuation in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.4.1.3.1	Serious TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.4.1.3.2	Serious TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.4.1.3.3	Serious TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.3.1.4.1.4.1	Serious TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.4.1.4.2	Serious TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.4.1.4.3	Serious TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.5.1.3.1	Treatment Related TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.5.1.3.2	Treatment-Related TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dose (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.5.1.3.3	Treatment Related TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.3.1.5.1.4.1	Treatment Related TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Mean	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Daily Dose (Cohort B - Japan)- OLE Safety Population		
Table	14.3.1.5.1.4.2	Treatment-Related TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Part 2 Modal Dosage (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.5.1.4.3	Treatment Related TEAEs in Part 2 by MedDRA System Organ Class, Preferred Term, and Dosage at Onset (Cohort B - Japan)- OLE Safety Population	N/A	Y
Table	14.3.1.6.1.3	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, Maximum Severity, and Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.6.1.4	Treatment-Emergent Adverse Events in Part 2 by MedDRA System Organ Class, Preferred Term, Maximum Severity, and Part 2 Mean Daily Dose (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.9.1.3.1	Treatment-Emergent Adverse Events of Special Interest (AESI) in Part 2 by System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.9.1.3.2	Treatment-Emergent Adverse Events of Special Interest (AESI) in Part 2 by System Organ Class, Preferred Term, and Part 2 Modal Dosage (Cohort A -	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		North America, Europe, Australia) - OLE Safety Population		
Table	14.3.1.9.1.3.3	Treatment-Emergent Adverse Events of Special Interest (AESI) in Part 2 by System Organ Class, Preferred Term, and Dosage at Onset (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.9.1.4.1	Treatment-Emergent Adverse Events of Special Interest (AESI) in Part 2 by System Organ Class, Preferred Term, and Part 2 Mean Daily Dose (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.9.1.4.2	Treatment-Emergent Adverse Events of Special Interest (AESI) in Part 2 by System Organ Class, Preferred Term, and Part 2 Modal Dosage (Cohort B - Japan) -OLE Safety Population	N/A	Y
Table	14.3.1.9.1.4.3	Treatment-Emergent Adverse Events of Special Interest (AESI) in Part 2 by System Organ Class, Preferred Term, and Dosage at Onset (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.1.10.1.1.1	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects in Any Dosage Group or Overall While Receiving ZX008 During Part 1 Through Part 2 by System Organ Class, Preferred Term, and Dosage at Onset with Number of Events and Number of Resolved Events (Cohort A - North America, Europe, Australia) - Long Term Safety Population	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.3.1.10.1.1.2	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects in Any Dosage Group or Overall While Receiving ZX008 During Part 1 Through Part 2 by System Organ Class, Preferred Term, and Dosage at Onset with Mean Onset and Mean Duration (Cohort A - North America, Europe, Australia) - Long Term Safety Population	Y	N/A
Table	14.3.1.10.1.1.3	Treatment-Emergent Adverse Events While Receiving ZX008 During Part 1 Through Part 2 by System Organ Class, Preferred Term, Concomitant Usage of Valproate, and Treatment Received During Part 1 (Cohort A - North America, Europe, Australia) - Long Term Safety Population	Y	N/A
Table	14.3.1.10.1.1.4	Treatment-Emergent Adverse Events While Receiving ZX008 During Part 1 Through Part 2 by System Organ Class, Preferred Term, and Concomitant Usage of Clobazam by Treatment Received During Part 1 (Cohort A - North America, Europe, Australia) - Long Term Safety Population	Y	N/A
Table	14.3.1.10.1.1.5	Treatment-Emergent Adverse Events While Receiving ZX008 During Part 1 Through Part 2 by System Organ Class, Preferred Term, and Most Common Combinations of AEDs, and Treatment Received During Part 1 (Cohort A - North America, Europe,	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Australia) - Long Term Safety Population		
Table	14.3.1.10.1.1.6	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects in Any Dosage Group or Overall During Part 2 by System Organ Class, Preferred Term, and Dosage at Onset with Number of Events and Number of Resolved Events (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.10.1.1.7	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects in Any Dosage Group or Overall During Part 2 by System Organ Class, Preferred Term, and Dosage at Onset with Mean Onset and Mean Duration (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.10.1.1.8	Treatment-Emergent Adverse Events with Onset During Part 1 that were Unresolved at the Start of Part 2 by System Organ Class, Preferred Term, and Treatment Received During Part 1 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.1.10.1.2.1	Treatment-Emergent Adverse Events That Occurred in at Least 10% of Subjects in Any Dosage Group or Overall While Receiving ZX008 During Part 1 Through Part 2 by Preferred Term, and Dosage at Onset with Number of Events and Number of	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Resolved Events (Cohort B - Japan) - Long Term Safety Population		
Table	14.3.1.10.1.2.2	Treatment-Emergent Adverse Events that Occurred in at Least 10% of Subjects in Any Dosage Group or Overall While Receiving ZX008 During Part 1 Through Part 2 by Preferred Term, and Dosage at Onset With Mean Onset and Mean Duration (Cohort B - Japan) - Long Term Safety Population	N/A	Y
~~Table~~	~~14.3.1.10.1.2.3~~	~~Treatment-Emergent Adverse Events While Receiving ZX008 During Part 1 Through Part 2 by System Organ Class, Preferred Term, Concomitant Usage of Valproate, and Treatment Received During Part 1 (Cohort B - Japan) - Long Term Safety Population~~	~~N/A~~	~~N~~
~~Table~~	~~14.3.1.10.1.2.4~~	~~Treatment-Emergent Adverse Events While Receiving ZX008 During Part 1 Through Part 2 by System Organ Class, Preferred Term, and Concomitant Usage of Clobazam by Treatment Received During Part 1 (Cohort B - Japan) - Long Term Safety Population~~	~~N/A~~	~~N~~
Table	14.3.1.10.1.2.5	Treatment-Emergent Adverse Events that Occurred in at Least 10% of Subjects in Any Dosage Group or Overall During Part 2 by System Organ Class, Preferred Term, and Dosage at Onset With Number of Events and Number of Resolved	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Events (Cohort B - Japan) - OLE Safety Population		
Table	14.3.1.10.1.2.6	Treatment-Emergent Adverse Events that Occurred in at Least 10% of Subjects in Any Dosage Group or Overall During Part 2 by System Organ Class, Preferred Term, and Dosage at Onset With Mean Onset and Mean Duration (Cohort B - Japan) - OLE Safety Population	**N/A**	**Y**
Table	14.3.1.10.1.2.7	Treatment-Emergent Adverse Events with Onset During Part 1 That Were Unresolved at the Start of Part 2 by System Organ Class, Preferred Term, and Treatment Received During Part 1 (Cohort B - Japan) - OLE Safety Population	**N/A**	**Y**
	14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**		
Table	14.3.2.1.2	Listing of Deaths in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.2.1.3	Listing of Deaths in Part 2 (Cohort B - Japan) - OLE Safety Population	Y	N/A
Table	14.3.2.2.3	Listing of SAEs in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.2.2.4	Listing of SAEs in Part 2 (Cohort B - Japan)	N/A	Y
Table	14.3.2.3.3	Listing of Discontinuations from Treatment or Study Due to AE in Part	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		2 (Cohort A - North America, Europe, Australia) - OLE Safety Population		
Table	14.3.2.3.4	Listing of Discontinuations from Treatment or Study Due to AE in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
	14.3.4	**Summary of Laboratory Data**		
Table	14.3.4.1.1.3	Laboratory Parameters in Part 2 - Hematology: Summary Statistics (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.1.1.4	Laboratory Parameters in Part 2 - Hematology: Summary Statistics (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.4.1.2.3	Shift Tables for Laboratory Parameters in Part 2 - Hematology (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.1.2.4	Shift Tables for Laboratory Parameters in Part 2 - Hematology (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.4.2.1.3	Laboratory Parameters in Part 2 - Chemistry: Summary Statistics (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.2.1.4	Laboratory Parameters in Part 2 - Chemistry: Summary Statistics (Cohort B - Japan) - OLE Safety Population	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.3.4.2.2.3	Shift Tables for Laboratory Parameters in Part 2 - Chemistry (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.2.2.4	Shift Tables for Laboratory Parameters in Part 2 - Chemistry (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.4.3.1.3	Laboratory Parameters in Part 2 - Urinalysis (Quantitative Parameters) : Summary Statistics (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.3.1.4	Laboratory Parameters in Part 2 - Urinalysis (Quantitative Parameters) : Summary Statistics (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.4.3.3.3	Shift Tables for Laboratory Parameters in Part 2 - Urinalysis (Quantitative Parameters) (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.3.3.4	Shift Tables for Laboratory Parameters in Part 2 - Urinalysis (Quantitative Parameters) (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.4.3.2.3	Laboratory Parameters in Part 2 - Urinalysis (Categorical Parameters): Summary Statistics (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.3.2.4	Laboratory Parameters in Part 2 - Urinalysis (Categorical Parameters):	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Summary Statistics (Cohort B - Japan) - OLE Safety Population		
Table	14.3.4.3.3.3	Shift Tables for Laboratory Parameters in Part 2 - Urinalysis (Categorical Parameters) (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.3.3.4	Shift Tables for Laboratory Parameters in Part 2 - Urinalysis (Categorical Parameters) (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.4.4.1.3	Laboratory Parameters in Part 2 - Tests of Precocious Puberty and Thyroid Function: Summary Statistics (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.4.1.4	Laboratory Parameters in Part 2 - Tests of Precocious Puberty and Thyroid Function: Summary Statistics (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.3.4.4.2.3	Shift Tables for Laboratory Parameters in Part 2 - Tests of Precocious Puberty and Thyroid Function (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.3.4.4.2.4	Shift Tables for Laboratory Parameters in Part 2 - Tests of Precocious Puberty and Thyroid Function (Cohort B - Japan) - OLE Safety Population	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
	14.4.1	**Vital Signs, Weight and BMI**		
Table	14.4.1.1.1.3	Vital Sign Parameters in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.4.1.1.1.4	Vital Sign Parameters in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.4.1.2.1.3	Body Height, Body Height Z-score, Body Weight, Body Weight Z-score, and Body Mass Index in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.4.1.2.1.4	Body Height, Body Height Z-score, Body Weight, Body Weight Z-score, and Body Mass Index in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.4.1.2.2.3	Weight Summary (Lost/Gain >=7% or >=10%) During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.4.1.2.2.4	Weight Summary (Lost/Gain >=7% or >=10%) During Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.4.1.2.2.5	Weight Summary (Lost/Gain >=7% or >=10%) During Part 2 by Part 1 Age Group (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.4.1.2.2.6	Weight Summary (Lost/Gain >=7% or >=10%) During Part 2 by Part 1 Age	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Group (Cohort B - Japan) - OLE Safety Population		
Figure	14.4.1.3.1.3	Spaghetti Plot of Weight by Part 2 Study Day for Subjects who had a >= 7% Decrease from Part 1 Baseline in Body Weight (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Figure	14.4.1.3.1.4	Spaghetti Plot of Weight by Part 2 Study Day for Subjects who had a >= 7% Decrease from Part 2 Baseline in Body Weight (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Figure	14.4.1.3.1.5	Spaghetti Plot of Weight by Part 2 Study Day for Subjects who had a >= 7% Decrease From Part 1 Baseline in Body Weight by Age Group (Cohort B - Japan) - OLE Safety Population	N/A	Y
Figure	14.4.1.3.1.6	Spaghetti Plot of Weight by Part 2 Study Day for Subjects who had a >= 7% Decrease From Part 2 Baseline in Body Weight by Age Group (Cohort B - Japan) - OLE Safety Population	N/A	Y
	14.4.4	**Tanner Staging**		
Table	14.4.4.3.1.1	Tanner Staging in Part 2 by Part 1 Age Group for Boys (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.4.4.3.1.2	Tanner Staging in Part 2 by Part 1 Age Group for Boys (Cohort B - Japan) - OLE Safety Population	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.4.4.4.1.1	Tanner Staging in Part 2 by Part 1 Age Group for Girls (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.4.4.4.1.2	Tanner Staging in Part 2 by Part 1 Age Group for Girls (Cohort B - Japan) - OLE Safety Population	N/A	Y
	14.4.5	**Columbia-Suicide Severity Rating Scale (C-SSRS)**		
Table	14.4.5.1.3	Columbia Suicide Severity-Rating Scale (C-SSRS) - Number of Subjects with Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior Without Suicidal Intent Based on the C-SSRS During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.4.5.1.4	Columbia Suicide Severity-Rating Scale (C-SSRS) - Number of Subjects with Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior Without Suicidal Intent Based on the C-SSRS During Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.4.5.2.3	Columbia Suicide Severity-Rating Scale (C-SSRS)- Shift Table of Changes in C-SSRS Categories During Part 1 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.4.5.2.4	Columbia Suicide Severity-Rating Scale (C-SSRS)- Shift Table of Changes in C-SSRS Categories During	N/A	Y

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Part 1 (Cohort B - Japan) - OLE Safety Population		
	14.4.6	**Brief Rating Inventory of Executive Function- (BRIEF)**		
Table	14.4.6.1.3	Brief Rating Inventory of Executive Function Preschool Version (BRIEF-P) in Part 2 by Treatment Received in Part 1: Scoring Summary Table (Cohort A - North America, Europe, Australia)- OLE Safety Population	Y	N/A
Table	14.4.6.1.4	Brief Rating Inventory of Executive Function Preschool Version (BRIEF-P) in Part 2 by Treatment Received in Part 1: Scoring Summary Table (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.4.6.2.3	Brief Rating Inventory of Executive Function (BRIEF) in Part 2 by Treatment Received in Part 1: Scoring Summary Table (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Table	14.4.6.2.4	Brief Rating Inventory of Executive Function (BRIEF) in Part 2 by Treatment Received in Part 1: Scoring Summary Table (Cohort B - Japan) - OLE Safety Population	N/A	Y
Table	14.4.6.3.3	Brief Rating Inventory of Executive Function (BRIEF-A) in Part 2 by Treatment Received in Part 1: Scoring Summary Table (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A

Table/ Figure	Number	Table Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Table	14.4.6.3.4	Brief Rating Inventory of Executive Function (BRIEF-A) in Part 2 by Treatment Received in Part 1: Scoring Summary Table (Cohort B - Japan) - OLE Safety Population	N/A	Y

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Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
	16.2	**Subject data listing**		
	16.2.1	**Subject disposition and discontinuation**		
Listing	16.2.1.1.3	Subject Completion/Discontinuation in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.1.1.4	Subject Completion/Discontinuation in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
	16.2.2	**Protocol deviations**		
Listing	16.2.2.1.3	Major Protocol Deviations in Part 2 (Cohort A - North America, Europe, Australia)	Y	N/A
Listing	16.2.2.1.4	Major Protocol Deviations in Part 2 (Cohort B - Japan)	N/A	Y
Listing	16.2.3.1.3	Part 2 Visits Conducted During the COVID-19 Period, Showing Completed Visits, Telemedicine Visits, Telephone Visits, Missed Visits, Missed Assessments, and Out of Window Visits (Cohort A - North America, Europe, Australia) OLE Safety Population	Y	N/A
Listing	16.2.3.1.4	Part 2 Visits Conducted During the COVID-19 Period, Showing Completed Visits, Telemedicine Visits, Telephone Visits, Missed Visits, Missed Assessments, and Out of	N/A	Y

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Window Visits (Cohort B - Japan) OLE Safety Population		
	16.2.4	**Demographic data and other baseline characteristics**		
Listing	16.2.4.1.1.3	Demographic data in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.4.1.1.4	Demographic data in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.4.1.4.3	% Change from Baseline in Weight and BMI in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.4.1.4.4	% Change From Baseline in Weight and BMI in Part 2 (Cohort B - Japan) OLE Safety Population	N/A	Y
Listing	16.2.4.2.1.3	Medical History and Neurologic History for Subjects in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.4.2.1.4	Medical History and Neurologic History for Subjects in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.4.2.3.3	Seizure History for Subjects in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.4.2.3.4	Seizure History for Subjects in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.4.3.2.3	Concomitant Medications and Therapies/Treatments for Subjects in	Y	N/A

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population		
Listing	16.2.4.3.2.4	Concomitant Medications and Therapies/Treatments for Subjects in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.4.4.2.3	Concomitant Antiepileptic Drugs (AEDs) for Subjects in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.4.4.2.4	Concomitant Antiepileptic Drugs (AEDs) for Subjects in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.4.5.1.3	Rescue Medications Used in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.4.5.1.4	Rescue Medications Used in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
	16.2.5	**Treatment exposure and compliance**		
Listing	16.2.5.1.3	IMP Intake per Day During Treatment in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.5.1.4	IMP Intake per Day During Treatment in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.5.2.3	IMP Intake - Self Reported % Compliance in Part 2 (Cohort A -	Y	N/A

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		North America, Europe, Australia) - OLE Safety Population		
Listing	16.2.5.2.4	IMP Intake - Self Reported % Compliance in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.5.3.3	Drug Accountability in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.5.3.4	Drug Accountability in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.5.4.3	Background Antiepileptic Drugs (AEDs) Pharmacokinetic Concentrations in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.5.4.4	Background Antiepileptic Drugs (AEDs) Pharmacokinetic Concentrations in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
	16.2.6	**Efficacy data**		
Listing	16.2.6.1.1.3	Recorded Seizures - Duration and Number of Occurrences per Subject in Part 2 (Diary data) (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.1.1.4	Recorded Seizures - Duration and Number of Occurrences per Subject in Part 2 (Diary data) (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.6.1.2.3	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline During Part 2(Cohort A	Y	**N/A**

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		- North America, Europe, Australia) - OLE Safety Population		
Listing	16.2.6.1.2.3a	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.1.2.3b	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.1.2.3c	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.1.2.4	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline During Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	**Y**
Listing	16.2.6.2.1.3	Clinical Global Impression - Improvement Rating as Assessed by the Investigator in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.2.1.4	Clinical Global Impression - Improvement Rating as Assessed by the Investigator in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Listing	16.2.6.2.2.3	Clinical Global Impression - Improvement Rating as Assessed by the Parent/Caregiver in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.2.2.4	Clinical Global Impression - Improvement Rating as Assessed by Parent/Caregiver in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.6.3.3	Change in Countable Motor Seizures from Baseline During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	N	**N/A**
Listing	16.2.6.3.4	Change in Countable Motor Seizures from Baseline During Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	N
Listing	16.2.6.4.3	Duration of Longest Interval Between Seizures in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	N	**N/A**
Listing	16.2.6.4.4	Duration of Longest Interval Between Seizures Resulting in Drops (ESC Confirmed) and Seizures that Typically Result in Drops in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.6.5.3	Change in Seizures that Typically Result in Drops from Baseline During Part 1 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.5.3a	Change in Seizures that Typically Result in Drops from Baseline During Part 2 (Cohort A - North America,		**N/A**

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Europe, Australia) (Pre-DCR Seizure Event Dataset Version 1) - OLE Safety Population		
Listing	16.2.6.5.3b	Change in Seizures that Typically Result in Drops from Baseline During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.5.3c	Change in Seizures that Typically Result in Drops from Baseline During Part 2 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.5.4	Change in Seizures that Typically Result in Drops From Baseline During Part 1 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.6.6.3	Change in Countable Non-Motor Seizures from Baseline During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	N	**N/A**
Listing	16.2.6.6.4	Change in Countable Non-Motor Seizures From Baseline During Part 2 (Cohort B - Japan) - OLE Safety Population OLE Safety Population	N/A	N
Listing	16.2.6.7.3	Change in All Countable Seizures (Motor + Non-Motor) from Baseline During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	N	**N/A**
Listing	16.2.6.7.4	Change in All Countable Seizures (Motor + Non-Motor) From Baseline	N/A	N

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		During Part 2 (Cohort B - Japan) - OLE Safety Population		
Listing	16.2.6.13.3	Change in Rescue Medication Usage from Baseline During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.13.4	Change in Rescue Medication Usage From Baseline During Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.6.14.3	Seizure-Free Days During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.6.14.4	Seizure-Free Days During Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.6.15.3	Hospitalizations and Medical Services (Cohort A - North America, Europe, Australia) - OLE Safety Population	N	**N/A**
Listing	16.2.6.15.4	Hospitalizations and Medical Services (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.6.17.3	Quality of Life in Childhood Epilepsy (QOLCE) Scale in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	N	**N/A**
Listing	16.2.6.17.4	Quality of Life in Childhood Epilepsy (QOLCE) Scale in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.6.18.3	Zarit Caregiver Burden Inventory in Part 2 (Cohort A - North America,	N	**N/A**

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		Europe, Australia) - OLE Safety Population		
Listing	16.2.6.18.4	Zarit Caregiver Burden Inventory in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	N
Listing	16.2.6.19.3	Parent/Caregiver Ratings using HADS Scale in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	N	N/A
Listing	16.2.6.19.4	Parent/Caregiver Ratings using HADS Scale in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	N
Listing	16.2.6.20.3	Change in Seizure of All Countable Seizures that did not Result in Drops (ESC Confirmed) Frequency Resulting in Drops (ESC Confirmed) from Baseline During Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.6.20.4	Change in Seizure of All Countable Seizures that did not Result in Drops (ESC Confirmed) Frequency Resulting in Drops (ESC Confirmed) From Baseline During Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.6.21.1	Investigator's Assessment of Seizure Burden After OLE Month 12 (Cohort B - Japan) - OLE mITT Population	N/A	Y
	16.2.7	**Adverse events**		
Listing	16.2.7.1.3	Adverse Events in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Listing	16.2.7.1.4	Adverse Events in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.7.2.3	Adverse Events of Special Interest (AESI) in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.7.2.4	Adverse Events of Special Interest (AESI) in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.7.3.1	Adverse Events with Onset in Part 1 that were Ongoing at the Start of Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.7.3.2	Adverse Events With Onset in Part 1 that Were Ongoing at the Start of Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.7.4.1	Adverse Events from Part 1 and Part 2 (Cohort A - North America, Europe, Australia) - Long Term Safety Population	Y	**N/A**
Listing	16.2.7.4.2	Adverse Events From Part 1 and Part 2 (Cohort B - Japan) - Long Term Safety Population	N/A	Y
	16.2.8	**Laboratory data**		
Listing	16.2.8.1.1.3	Laboratory Data Hematology Parameters in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Listing	16.2.8.1.1.4	Laboratory Data Hematology Parameters in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.8.1.2.3	Extreme Value Laboratory Parameters - Hematology in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.8.1.2.4	Extreme Value Laboratory Parameters - Hematology in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.8.2.1.3	Laboratory Data Biochemistry Parameters in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.8.2.1.4	Laboratory Data Biochemistry Parameters in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.8.2.2.3	Extreme Value Laboratory Parameters in Part 2- Biochemistry (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.8.2.2.4	Extreme Value Laboratory Parameters in Part 2- Biochemistry (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.8.3.1.3	Laboratory Data Coagulation Parameters in Part 1 and Part 2 (Cohort A - North America, Europe, Australia) OLE Safety Population	N	**N/A**
Listing	16.2.8.3.1.4	Laboratory Data Coagulation Parameters in Part 1 and Part 2	**N/A**	N

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
		(Cohort B - Japan) OLE Safety Population		
Listing	16.2.8.4.1.3	Laboratory Data Urinalysis Parameters in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.8.4.1.4	Laboratory Data Urinalysis Parameters in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.8.4.2.3	Extreme Value Urinalysis Data in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.8.4.2.4	Extreme Value Urinalysis Data in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.8.5.3	Tests of Growth, Precocious Puberty and Thyroid Function in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.8.5.4	Tests of Growth, Precocious Puberty and Thyroid Function (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.8.6.3	Urine and Serum Pregnancy tests in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.8.6.4	Urine and Serum Pregnancy tests in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Listing	16.2.8.7.3	Urine and Serum THC Panel in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.8.7.4	Urine and Serum THC Panel in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.8.8.3	Laboratory Data: Listing of Test Comments from Lab Vendor for All Laboratory Parameters Collected in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.8.8.4	Laboratory Data: Listing of Test Comments From Lab Vendor for All Laboratory Parameters Collected in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
	16.2.9	**Other Safety Data**		
Listing	16.2.9.1.1.3.1	Vital Signs in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.9.1.1.3.2	Body Height, Body Height Z-Score, Body Weight, Body Weight Z-Score, and BMI in Part 2 (Cohort A - North America, Europe, Australia)) - OLE Safety Population	Y	**N/A**
Listing	16.2.9.1.1.4.1	Vital Signs in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	**Y**
Listing	16.2.9.1.1.4.2	Body Height, Body Height Z-Score, Body Weight, Body Weight Z-Score, and BMI in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Listing	16.2.9.1.2.3	Abnormal Vital Signs Data in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.9.1.2.4	Abnormal Vital Signs Data in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.9.2.3	Columbia-Suicide Severity Rating Scale (C-SSRS) for Subjects with Reported Suicidal Ideation or Suicidal Behavior in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.9.2.4	Columbia-Suicide Severity Rating Scale (C-SSRS) for Subjects with Reported Suicidal Ideation or Suicidal Behavior in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.9.3.1.3	Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P) in Part 2- Individual Questions (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A
Listing	16.2.9.3.1.4	Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P) in Part 2- Individual Questions (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.9.3.2.3	Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P) in Part 2- Summary Scales and Indexes (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	N/A

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Listing	16.2.9.3.2.4	Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P) in Part 2- Summary Scales and Indexes (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.9.3.3.3	Behavior Rating Inventory of Executive Function (BRIEF) in Part 2- Individual Questions (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.9.3.3.4	Behavior Rating Inventory of Executive Function (BRIEF) in Part 2- Individual Questions (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.9.3.4.3	Behavior Rating Inventory of Executive Function (BRIEF) in Part 2- Summary Scales and Indexes (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.9.3.4.4	Behavior Rating Inventory of Executive Function (BRIEF) in Part 2- Summary Scales and Indexes (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.9.3.5.3	Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) in Part 2- Individual Questions (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.9.3.5.4	Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) in Part 2- Individual Questions (Cohort B - Japan) - OLE Safety Population	N/A	**Y**

Listing	Number	Listing Header	Included in sNDA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)	Included in PCA Interim Analysis (Y= Yes, N = No, N/A = Not applicable)
Listing	16.2.9.3.6.3	Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) in Part 2- Summary Scales and Indexes (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.9.3.6.4	Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) in Part 2- Summary Scales and Indexes (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.9.4.3	Tanner Staging in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.9.4.4	Tanner Staging in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y
Listing	16.2.9.5.3	Physical Examination and Neurologic Examination in Part 2 (Cohort A - North America, Europe, Australia) - OLE Safety Population	Y	**N/A**
Listing	16.2.9.5.4	Physical Examination and Neurologic Examination in Part 2 (Cohort B - Japan) - OLE Safety Population	N/A	Y

19 Appendices

19.1 Appendix 1 – Seizure Types

1. All Seizures	2. Countable Motor Seizures	3. Countable Non-Motor Seizures	4. Drop Seizures (ESC confirmed or Typical)	5.Non-drop Seizures
Generalized Tonic-Clonic	Generalized Tonic-Clonic		Generalized Tonic-Clonic	Generalized Tonic-Clonic (not ESC confirmed)
Secondarily Generalized Tonic-Clonic	Secondarily Generalized Tonic-Clonic		Secondarily Generalized Tonic-Clonic	Secondarily Generalized Tonic-Clonic (not ESC confirmed)
Tonic	Tonic		Tonic	Tonic (not ESC confirmed)
Atonic	Atonic		Atonic	Atonic (not ESC confirmed)
Tonic/Atonic	Tonic/Atonic		Tonic/Atonic	Tonic/Atonic (not ESC confirmed)
Clonic	Clonic			Clonic
Hemiclonic	Hemiclonic			Hemiclonic
Focal with clear observable signs	Focal with clear observable signs			Focal with clear observable signs
Focal without clear observable signs		Focal without clear observable signs		Focal without clear observable signs
Myoclonic		Myoclonic		Myoclonic
Absence/atypical absence		Absence/atypical absence		Absence/atypical absence
Infantile Spasms		Infantile Spasms		Infantile Spasms
Epileptic Spasms		Epileptic Spasms		Epileptic Spasms

1. All Seizures	2. Countable Motor Seizures	3. Countable Non-Motor Seizures	4. Drop Seizures (ESC confirmed or Typical)	5.Non-drop Seizures
Other		Other		Other

19.2 Appendix 2 - Seizure Classification – Primary Endpoint

The primary endpoint for Study 1601 is defined as the change from baseline in seizures that result in drops. Seizures that result in drops include those of type: atonic, tonic, tonic/atonic, and tonic clonic (i.e., generalized tonic clonic, and secondarily generalized tonic clonic). The seizures that result in drops are similar to those as defined in the Epidiolex Phase 3 clinical studies GWPCARE3 and GWPCARE4, which were atonic, tonic, or tonic clonic (Devinsky 2018, Thiele 2018).

In the Statistical Analysis Plan (SAP) version 1.0 dated 5 August 2019, seizures resulting in drops were defined as those of the five types listed above and specified in the DSD as seizures that result in a fall based on a "Yes" response to Question 9 in the DSD. During study conduct a large number of data clarifications were raised for Question 9 leading to the conclusion that there was uncertainty amongst caregivers in how to properly answer the question. Based on this uncertainty, the definition of seizures that result in drops was changed to those of the five pre-specified types that have been reviewed and approved for each subject as a "drop seizure" by the Epilepsy Study Consortium (ESC). Approval is based on the seizures for each subject submitted to the ESC on the Seizure Identification Form during the Baseline Visit and logged in the eCRF on the Seizure History Form.

Thus, in the Part 1 SAP, drop seizures for the primary analysis will be those of the pre-specified type that have been approved for an individual subject as Drop by the ESC as indicated on the Seizure History eCRF under variable DROP_ and captured in the seizure diary.

For Cohort A, under this definition, classifying a particular seizure in the diary as a drop seizure requires determining whether the type of seizure in question has been identified in the Seizure History eCRF as a drop seizure for that subject. This can typically be done by matching a seizure type identifier in the diary to its counterpart in the Seizure History eCRF. Specifically, each seizure type entered into the Seizure History eCRF is identified by a "Record Position" number. These seizure types are then referred to by subjects or caregivers when recording seizures into the electronic Seizure Diary where they are labeled with a "Seizure Unique ID". For most subjects, there is a direct correspondence between the Seizure Unique ID in the seizure diary and the Record Position number on the Seizure History eCRF. However, for some subjects the correspondence is imperfect and aligning seizure types between the diary and the Seizure History eCRF requires an examination of text fields. In order to ensure that drop seizures are properly classified, a manual reconciliation between the Record Position number and the Seizure Unique

ID was performed. The reconciliation resulted in a list of ESC-approved drop seizures for each subject from which the seizures entered in the DSD would be compared against in order to identify seizures for the primary endpoint. In order to facilitate seizure selection the list generated from the reconciliation was entered into a separate database and transferred to the study database via data transfer specifications.

The procedures for the reconciliation are described in an addendum to the Data Management Plan.

19.3 Appendix 3 – Clinically Significant Vital Sign Abnormalities

Parameter	Age Group	Abnormally Low	Abnormally High	Change Criteria
Weight (kg)	All			Lost more than 7% of baseline weight or Gained more than 7% of baseline weight
Heart Rate (beats / minute)	2	< 87	> 150	Absolute Change from baseline > 20 bpm
	3	< 82	> 146	Absolute Change from baseline > 20 bpm
	4-5	< 77	> 142	Absolute Change from baseline > 20 bpm
	6-7	< 71	> 137	Absolute Change from baseline > 20 bpm
	8-11	< 66	> 129	Absolute Change from baseline > 20 bpm
	12-14	< 61	> 121	Absolute Change from baseline > 20 bpm
	15-17	< 57	> 115	Absolute Change from baseline > 20 bpm
	18-100	<60	>100	Absolute Change from baseline > 20 bpm
Systolic Blood Pressure (mmHg)	2-4	< 85	> 100	Absolute Change from baseline > 20 mmHg
	5-11	< 90	> 110	Absolute Change from baseline > 20mmHg
	12-17	< 100	> 120	Absolute Change from baseline > 20 mmHg
	18-100	<90	>130	Absolute Change from baseline > 20 mmHg
Diastolic Blood Pressure (mmHg)	2-4	< 40	> 64	Absolute Change from baseline > 10 mmHg
	5-11	< 51	> 75	Absolute Change from baseline > 10 mmHg
	12-17	< 61	> 80	Absolute Change from baseline > 10 mmHg

Parameter	Age Group	Abnormally Low	Abnormally High	Change Criteria
	18-100	<60	>85	Absolute Change from baseline > 10 mmHg
BMI (kg/m**2)	2-17	<= 20	>= 25	
	18-100	<= 20	>= 30	
Temperature (°C)	2-100	<= 36	>= 38	

SAP_1601_Part_2_Cohort_B_11OCT2022_CLEAN_zogenix signatures

Final Audit Report 2022-11-15

Created:	2022-11-15
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PART 2 STATISTICAL ANALYSIS PLAN FOR CARDIOVASCULAR ENDPOINTS

Study Title:	A Two-Part Study of ZX008 in Children and Adults with Lennox-Gastaut Syndrome (LGS); Part 1: A Randomized, Double-blind, Placebo-controlled Trial of Two Fixed Doses of ZX008 (Fenfluramine Hydrochloride) Oral Solution as Adjunctive Therapy for Seizures in Children and Adults with LGS, Followed by Part 2: An Open-label Extension to Assess Long-Term Safety of ZX008 in Children and Adults with LGS
Investigational Product:	ZX008
Sponsor Study No.:	ZX008-1601
SAP Status:	Final V2.0
Date of SAP:	22 FEB 2023
SAP Prepared by:	ERT
Sponsor:	Zogenix International Limited A wholly owned subsidiary of UCB Biosciences, Inc. 4000 Paramount Pkwy, Suite 200 Morrisville, NC 27560, USA

SAP Approvals

ERT

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Signer Name: [redacted]
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02-Mar-2023 | 17:28:44 CET
Date

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06-Mar-2023 | 08:06:42 PST
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02-Mar-2023 | 09:00:20 PST
Date

Consulting Biostatistician

UCB

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02-Mar-2023 | 07:54:16 PST
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Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 02-Mar-2023 | 20:38:43 PST
[redacted]4527504B
Statistician on behalf of UCB

02-Mar-2023 | 20:38:51 PST
Date

Table of Contents

Abbreviations and Definitions of Terms

ΔHR	Change from baseline in Heart Rate
ΔPR	Change from baseline in the PR-interval
ΔQRS	Change from baseline in the QRS duration
ΔQTcF	Change from baseline in the QTcF interval
ACI	Abnormal Clinically Insignificant
APCS	Abnormal Potentially Clinically Significant
bpm	Beats per minute
CAMI	Computer Assisted Measurement of Intervals
CI	Confidence Interval
DSF	Drop Seizure Frequency
ECHO	Echocardiograms
ECG	Electrocardiogram
EOS/ET	End of Study/Early Termination
GSMB	Global Superimposed Median Beat
kg	Kilogram
HR	Heart Rate
LGS	Lennox-Gastaut Syndrome
mg	Milligram
mm	Millimeter(s)
mmHg	Millimeters of Mercury
ms	Millisecond(s)
OLE	Open Label Extension
PASP	Pulmonary Artery Systolic Pressure
PR	Interval between the start of the P wave and start of the Q wave
QRS	QRS waves complex on the electrocardiogram tracing
QT	Interval between the start of the Q wave and the end of the T wave
QTc	Corrected QT duration
QTcF	QT interval corrected using Fridericia's formula
RR	The time interval between consecutive heart beats.
SAP	Statistical Analysis Plan
SD	Standard Deviation
STP	Stiripentol
TdP	Torsade de Pointes
VHD	Valvular heart disease
ZX008	Fenfluramine Hydrochloride

1. Introduction

1.1 Changes Made from Version 1.0 of the Part 2 SAP for Cardiovascular Endpoints

This SAP – specifying analyses of cardiovascular endpoints in Study 1601Part 2 – has been revised primarily to accommodate visit schedule changes introduced in Amendment 4.0 (Japan, 25-Jul-2022) of the study protocol. Specifically, the revision updates Version 1.0 of the Part 2 cardiovascular SAP to accommodate additional visits described in the Amendment 4.0 that could allow subjects in Part 2 Cohort B to potentially extend their participation in the study for up to 5 years.

The following is a list of other changes:

- Descriptions of 2 interim analyses have been added. The first facilitates regulatory submissions in the U.S. and Europe and the second supports a regulatory submission in Japan.
- The background section has been updated to describe more recent results from clinical trials of ZX008.
- A description has been added of a summary of missed or delayed visits due to COVID-19.
- Corrections were made to some titles of tables, figures, and listings (TFLs), and TFLs that had been left out of the previous version of the SAP were added.

Note that the objectives and endpoints have not been changed, i.e., they are identical to those specified in Version 1.0 of the cardiovascular SAP.

1.2 Background

Study ZX008-1601 is investigating ZX008, an oral solution of fenfluramine hydrochloride, for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS).LGS is a rare epileptic encephalopathy. The onset of LGS occurs most commonly before age 11, with a peak between 3 and 5 years of age (Arzimanoglou 2009; Hancock 2013). Patients with LGS account for 5 to 10% of children with seizures (Panayiotopoulos 2005).The most common seizure types are generalized tonic-clonic seizures, tonic seizures, atonic seizures, and tonic/atonic seizures, all of which most often can result in “drop attacks.” Other seizure types that occur in some LGS patients include atypical absences, nonconvulsive seizures, focal seizures, and myoclonic seizures. Nearly all patients have treatment-resistant, lifelong epilepsy. Patients with LGS have a poor prognosis: 5% of children die, 80 to 90% continue having seizures into adulthood, and nearly all have cognitive and behavioral problems (Panayiotopoulos 2005). Children and adults with LGS have an enormous impact on their families and efforts to improve the quality of life for these subjects are complex.

Fenfluramine is a serotonin releasing agent and increases the availability of extracellular serotonin by binding to the serotonin transporter protein and by being taken into the nerve terminal, where it disrupts vesicles, causing a release of serotonin into the extracellular space. It reverses the serotonin transporter function to promote serotonin release rather than uptake. In vivo and in vitro studies conducted by Zogenix suggest that fenfluramine reduces seizures by acting as an agonist at the 5-HT1D and 5-HT2C receptors and by acting as a positive allosteric modulator on the sigma-1 receptor; studies have shown positive allosteric modulators of sigma-1 reduce seizures in animal models. Fenfluramine may also exert antiseizure activity through the 5-HT1A and 5-HT2A receptors and possibly other yet to be identified mechanisms.

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

Valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) are important potential risks to monitor with ZX008 treatment based on the previously reported cardiotoxicity associated with fenfluramine treatment for adult obesity, commonly in combination with phentermine, at doses of 60 to 120 mg/day: i.e., 2 to 4 times higher than the proposed maximum daily dose for Dravet syndrome and LGS. The ZX008 clinical development program includes a prospectively-defined, long-term longitudinal cardiovascular study of the function and structure of the heart valves, focusing on signs of VHD and PAH. Safety assessment in the ZX008 clinical program includes serial color Doppler ECHOs to monitor for VHD (valvulopathy) and PAH. Study 1603, a thorough QT study in healthy adult subjects was also conducted. This ECHO program was designed with input from FDA and from cardiology experts.

In addition to LGS, Zogenix is investigating ZX008 for the treatment of seizures associated with Dravet syndrome. Zogenix has reported safety and efficacy data from 3 adequate and well controlled studies in patients with Dravet syndrome, Study 1, Study 2 (previously referred to as Study 1504 Cohort 2), and Study 3. Study 1 and Study 3 compared 2 doses of ZX008, 0.2 mg/kg/day and 0.8 mg/kg/day (up to a maximum of 30 mg/day), to

placebo in subjects receiving standard of care anti-epileptic treatments excluding stiripentol (STP). Study 2 compared a dose of ZX008 0.5 mg/kg/day (up to a maximum of 20 mg/day) to placebo in subjects receiving standard of care anti-epileptic treatments where administration of STP (in combination with clobazam [CLB] and/or valproate [VPA]; i.e., the STP regimen) was mandatory.

All studies met the primary efficacy endpoint and all key secondary efficacy endpoints. In all studies, a highly statistically significant reduction in monthly convulsive seizure frequency was achieved in subjects randomized to receive ZX008 in addition to their standard of care antiepilepsy treatments compared to placebo. Results from these Phase 3 studies demonstrated that ZX008 had an acceptable safety profile and was well tolerated at doses up to 30 mg/day administered in the ZX008 clinical program.

There have been no observed signs of cardiotoxicity associated with ZX008 in the Dravet Syndrome and LGS clinical development programs, and this continues to be true as of November 2021. Repeated ECHOs using an ECHO core laboratory review have not revealed any cardio toxic effects. Two subjects in the LGS program, (an [redacted]-year-old [redacted] and a [redacted]-year-old [redacted]) had ECHOs showing mild AR without evidence of valvular heart disease (VHD), with no changes in aortic valve morphology or abnormal valve movement observed on any ECHO. Both subjects had follow-up transthoracic ECHOs and the [redacted]-year old subject also had follow-up transesophageal ECHOs (TEEs) that demonstrated the aortic valves were structurally normal, with no morphological changes or restricted leaflet movement. While these 2 subjects met the US Food and Drug Administration (FDA) case definition of cardiac valvulopathy by grade of aortic valve regurgitation (AR), at no time was there any clinical or echocardiographic evidence of VHD for these subjects. Only LGS subjects ≥18 years of age had mild MR. These point prevalence results are consistent with published literature (Webb 2015).

This Statistical Analysis Plan (SAP) for Cardiovascular Endpoints outlines the planned analyses to support the assessment of electrocardiographic (ECG) and echocardiographic data for Part 2 of the trial. The planned analyses identified in this SAP may be included in regulatory submissions, and exploratory analyses not defined in this SAP may be performed to support a more thorough understanding of the safety data. All post-hoc or unplanned analyses performed not identified in this SAP will be documented.

Documents used to develop this SAP for Part 2 of the trial are:

- Zogenix ZX008-1601 Part 2 Statistical Analysis Plan for Cardiovascular Endpoints (Version 1.0, 25 August 2020).
- Zogenix ZX008-1601 Part 1 Statistical Analysis Plan for Cardiovascular Endpoints (Final Version 2.0. 01 March 2022).
- Syneos Health-Zogenix ZX008-1601 Part 2 Statistical Analysis Plan (Version 5.0, 12 October 2022).
- Study Protocol ZX008-1601 (2 July 2020, Amendment 3.1).
- Study Protocol ZX008-1601 (25 July 2022, Amendment 4.0 Japan)
- ZX008 Investigational Brochure (Version 10.0, 01 September 2022).

The analyses for Cardiovascular Endpoints of Part 1 are detailed in the signed SAP dated 01MAR2022.

2. Study Design and Cardiovascular Analysis Objectives

2.1 General Design and Plan

Study ZX008-1601 is an international multicenter study being conducted in two parts. Up to approximately 80 study sites in North America, Europe, Australia, and Japan are planned to participate. Part 1 is a double-blind, parallel-group, placebo-controlled, study to assess the efficacy and safety of two doses of ZX008 when used as adjunctive therapy for seizures in children and adult subjects with LGS. Part 2 is an open-label extension to assess long-term safety of ZX008. Parts 1 and 2 will include 2 cohorts: Cohort A will include subjects from North America, Europe, and Australia; Cohort B will include subjects from Japan.

Each subject in Part 1 is assigned to one of 2 treatments (0.2 mg/kg or 0.8 mg/kg) or placebo groups. Treatments were assigned on a 1:1:1 basis. Part 2 consists of open-label, flexible dosing up to 0.8 mg/kg/day (30mg/day maximum).

For subjects in Part 2 Cohort A,ECG and ECHO data will be collected on Study Day 1, Months 1, 3, 6, 9, and 12 (EOS/ET).

Subjects in Cohort B have the option to receive ZX008 for up to 72months (plus a 2-week taper at the end of the Part 2), or until ZX008 is approved in the subject's country of residence and listed on a patient's health plan formulary, whichever occurs first. Specifically, if marketing approval is not yet received after the end of the Part 2 Treatment Period, treatment may be extended on an annual basis in order to provide continuity of treatment for

subjects. Up to 5 annual extensions can be applied for a total treatment time of 72 months in Part 2. Subjects will return to the clinic every 6 months and have a phone visit 3 months after the in-clinic visit for each 1-year extension up to Month 72. Thus, for subjects in Cohort B, ECG and ECHO data will be collected on Study Day 1, Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, and 72 (EOS/ET for cohort B).

For both Cohort A and Cohort B, ECG is also collected on Month 2.

Cardiac follow-up visits, for subjects who discontinue study drug, will be conducted at least 3 and 6 months after the last dose, with additional follow-ups performed based on regional requirements. Data to be included in the analysis will be all available data up to the cutoff date determined for the main study analyses. All other study results for these subjects (demographics, efficacy, safety, PK) will be presented in the Clinical Study Report for ZX008-Study 1601 Part 2.

The ECHO Analysis Plan defined a threshold for PAH as any PASP greater than 35 mmHg. The ZX008 program employed usual clinical practice that any abnormal PASP findings were to be confirmed by repeat ECHO. If elevated PASP was not confirmed on repeat ECHO then a subject was not considered to have PAH.

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

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

Electrocardiograms will be reviewed by two, board-certified cardiologists. In the case of a discrepancy between the readers, the echocardiogram was sent to adjudicators for final reading. At the initiation of the ZX008 Program, the International (Pediatric) Cardiology Advisory Board (ICAB) was set-up to oversee the vendor's ECHO readings. ICAB members were chosen solely based on their academic credentials and experience, with the Chair being chosen based upon his/her seniority and respect in the field of echocardiography. When there is a differing interpretation of findings in an ECHO of any subject between the vendor and ICAB (either in the alert level of valvular regurgitation or presence or absence of pulmonary hypertension), the following process will occur: a telephone conference call will be held with the vendor ERT cardiology readers and ICAB reader and ICAB Chair (if the Chair was reader, then only he/she will be on call) to discuss the ECHO findings and try to come to an agreement on interpretation; if agreement cannot be reached then ICAB Chair will read the ECHO and his/her reading will become the official reading. This one ECHO report will then be sent to the IDSMC.

2.2 Objectives

The primary objective of Part 2 is to assess the long-term safety and tolerability of ZX008 in children and adults with LGS with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, cognition (Behavior Rating Inventory for Executive Function), vital signs (blood pressure, heart rate, temperature, and respiratory rate), ECG, ECHO, body weight, and BMI.

2.2.1. Cardiovascular Safety Objectives

The overall cardiovascular safety objective is to evaluate the long-term effects of ZX008 on the heart as demonstrated by both the 12-lead ECG and ECHO.

The main objective of the echocardiogram analysis is to evaluate the long-term effect of ZX008 on left-sided cardiac valves, with specific focus on the development of VHD. Other objectives are to evaluate the effect of ZX008 on the right-sided valves and PAH.

The main objective of the electrocardiographic analysis is to evaluate the long-term effect of ZX008 0.8 mg/kg/day (max 30 mg/day) on cardiac repolarization. Other objectives are to evaluate the effect of ZX008 on electrical activity of the heart such as AV conduction, cardiac depolarization, heart rate, and abnormal heart rhythm (arrhythmias).

Variables included in the analysis are listed below.

2.3 Endpoints

2.3.1 Echocardiograms

2.3.1.1 Main Echocardiographic Endpoint

The main endpoint of the echocardiographic analysis is the regurgitation score for the mitral and aortic valves at each time point with the main focus being the number of subjects who develop clinically meaningful (pathologic) changes in valve regurgitation with administration of ZX008, as measured by:

- Number of subjects who meet the FDA case definition of drug associated valvulopathy: aortic regurgitation ≥ mild and/or mitral regurgitation ≥ moderate
- Number of subjects with ≥ trace mitral or aortic regurgitation at least one time in Part 2
- Number of subjects with ≥ trace mitral or aortic regurgitation at end of study
- Number of subjects within each mitral or aortic regurgitation score by visit
- Number of subjects with clinically confirmed Valvular heart disease (VHD)

2.3.1.2 Other Echocardiographic Endpoints

Other endpoints include:

- Number of subjects within each tricuspid or pulmonic regurgitation score by visit
- Number of subjects with normal or trace tricuspid or pulmonic regurgitation at baseline and ≥ mild tricuspid or pulmonic regurgitation at end of study
- Pulmonary Artery Systolic Pressure (PASP)
    - Mean change from baseline at end of study
    - Mean maximum change from baseline at anytime during Part 2
    - Number of subjects with change from baseline at anytime during Part 2 of:
        - > 10 mmHg
        - > 15 mmHg
        - > 20 mmHg
    - Number of subjects at anytime during Part 2 with
        - PASP > 35 mmHg
- Right ventricular outflow tract(RVOT) (will be used only as confirmatory variables for pulmonary hypertension)
    - Mean Change from Baseline in RVOT (mmHg) by visit
    - Number of patients with Baseline ≥ 100 ms and at EOS/ET RVOT < 100 ms
    - Number of patients with any RVOT measurement < 100 ms post-baseline

Summary of the number of ECHOs per subject will be presented.

2.3.1.3 Heat Maps

Heat maps will be constructed for all valve scores to visualize longitudinal changes, if any, in regurgitation measures in individual subjects over time. An example of a heat map is shown below.

Cohort	Subjects	Study Day 1	Month 1, …, 36, 3 Month Follow-up	6 Month Follow-up
A	2 subjects	Absent	…	ECHO
A	5 subjects	Absent	…	Trace
A	1 subject	Absent	…	Trace
B	4 subjects	Absent	…	Absent
….				

Note: different colors represent the valve scores such as No ECHO, Absent, Absent, Mild, Moderate, and Severe.

Heat maps will be constructed for all valve scores by age groups (≤ 18, > 18 years).

2.3.2 ECG

2.3.2.1 Main ECG Endpoint

The main endpoint of the ECG analysis will be the mean change between measurements of QT interval corrected using Fridericia's formula (QTcF) for ZX008after baseline adjustment (ΔQTcF).

2.3.2.2 Other ECG Endpoints

Other endpoints include:

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

Age	Gender	Values
0 to < 12 years	Males and Females	< 320 ms
		≥ 320 ms to ≤ 450 ms
		> 450 ms to ≤ 480 ms
		> 480 ms
12 to < 18 years	Males	< 320 ms
		≥ 320 ms to ≤ 450 ms
		> 450 ms to 500 ms
		> 500 ms
12 to < 18 years	Females	< 320 ms
		≥ 320 ms to ≤ 470 ms
		> 470 ms to ≤ 500 ms
		> 500 ms
18 to 35 years	Males	< 320 ms
		≥ 320 ms to ≤ 450 ms
		> 450 ms to 500 ms
		> 500 ms
18 to 35 years	Females	< 320 ms
		≥ 320 ms to ≤ 470 ms
		> 470 ms to ≤ 500 ms
		> 500 ms

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

Age	Gender	Values
2 to < 6 years	Males and Females	≤ 90 ms
		> 90 ms to ≤ 100 ms
		> 100 ms
6 to < 12 years	Males and Females	≤ 100 ms
		> 100 ms to ≤ 110 ms
		> 110 ms
12 to < 18 years	Males and Females	≤ 110 ms
		> 110 ms to ≤ 120 ms
		>120 ms
18 to 35 years	Males and Females	≤ 120 ms
		> 120 ms

    - PR (number and percentage of subjects, by regimen and visit)

Age	Gender	Values
2 to < 6 years	Males and Females	≤ 90 ms

		> 90 ms to ≤ 150 ms
		> 150 ms
6 to < 12 years	Males and Females	≤ 100 ms
		> 100 ms to ≤ 170 ms
		> 170 ms
12 to < 18 years	Males and Females	≤ 110 ms
		> 110 ms to ≤ 180ms
		> 180 ms
18 to 35 years	Males and Females	≤ 120 ms
		> 120 ms to ≤ 220ms
		> 220 ms

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

Age	Gender	Values
2 to < 6 years	Males and Females	< 80 bpm
		≥ 80 bpm to ≤ 140 bpm
		> 140 bpm to ≤ 180 bpm
		> 180 bpm Increase or decrease from baseline > 10 bpm Increase or decrease from baseline > 20 bpm
6 to < 12 years	Males and Females	< 60 bpm
		≥ 60 bpm to ≤ 120 bpm
		> 120 bpm to ≤ 150 bpm
		> 150 bpm Increase or decrease from baseline > 10 bpm Increase or decrease from baseline > 20 bpm
12 to < 18 years	Males and Females	< 50 bpm
		≥ 50 bpm to ≤ 100 bpm
		> 100 bpm to ≤ 150 bpm
		> 150 bpm Increase or decrease from baseline > 10 bpm Increase or decrease from baseline > 20 bpm
18 to 35 years	Males and Females	< 50 bpm
		≥ 50 bpm to ≤ 100 bpm
		> 100 bpm to ≤ 150 bpm
		> 150 bpm Increase or decrease from baseline > 10 bpm Increase or decrease from baseline > 20 bpm

- Overall characterization of normal and abnormal ECGs and the number and percentage of subjects with normal and abnormal ECGs. ECGs will be characterized as Normal, Abnormal Clinically Insignificant (ACI), or Abnormal Potentially Clinically Significant (APCS). The number and percentage of ECGs within each category will be calculated by cohort and visit.
- Events for specific arrhythmias: Torsade de Pointes (TdP), ventricular tachycardia/fibrillation, atrial fibrillation/flutter, supraventricular tachycardia, etc., including associations between specific ECG findings and selected clinical adverse events of interest will be explored as appropriate

(events that may signal pro-arrhythmia: syncope, palpitations, dizziness, tachycardia, etc.).

2.3.2.3 Listing for Abnormalities

Listings for ECG abnormalities by cohort and visit will be provided for the following:

- Heart Rates
  - Sinus Tachycardia
  - Sinus Bradycardia
- PR-Interval
  - First degree AV-Block
  - Short PR interval
- Heart Blocks
  - Second degree AV-Block (Type 1)
  - Second degree AV-Block (Type 2)
  - Third-degree (complete) AV-Block
- QRS Duration
  - LBBB
  - RBBB
- QT-Interval
- Other abnormalities seen by the over-reading cardiologist, including changes in the T-wave morphology, MI, etc.

2.4 Study Population

Study ZX008-1601 includes male and female subjects, ages 2 to 35 years who met the inclusion and exclusion criteria in the protocol.

2.4.1 Sample Size

The sample size of Part 2 will be determined by the number of subjects in Part 1 who are eligible for and meet the necessary criteria for Part 2. The assumptions for the sample size in Part 1 are provided in the Part 1 SAP.

2.5 Randomization and Treatments

The description of the treatment assignment for Part 1 is provided in the Part 1 SAP. Part 2 of the study is open-label.

3. Cardiac Safety Data Collection and Analysis

3.1 ECG Assessment

3.1.1 Equipment

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

3.1.2 Transfer of ECGs

Electrocardiograms were digitally transferred to ERT for analysis.

3.1.3 Collection of ECGs

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

Single, 12-lead ECGs in Part 2 were collected on Study Day 1, Months 1, 2, 3, 6, 9, 12 (EOS/ET), and 3 and 6 months follow-up for Cohort A; and on Study Day 1, Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, and 72 (EOS/ET), and 3 and 6 months follow-up for Cohort B.

ECGs were collected after the subjects had been in supine position resting for ≥ 5 minutes.

The time of the ECG was not controlled.

3.1.4 Definition of Baseline

The OLE Baseline value in Part 2 is defined as the last ECG assessment on or before the first dose in the open-label period. In most cases, this will be the value obtained at Visit 15. Unscheduled assessments prior to First Dose Date in Part 2 will be considered for selection of the baseline values.

The pre-ZX008 Baseline (Core Baseline) is defined as the last ECG assessment on or before the first dose in Part 1.

3.1.5 Variables Measured

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

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

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

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

  Fridericia's correction: $QTcF = \frac{QT}{RR^{1/3}}$ where QT, RR, and QTcF are expressed in seconds.

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

3.1.6 Clinical Analysis of ECGs

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

3.1.7 Non-Digital ECG Evaluation

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

3.2 Echocardiographic Analysis

3.2.1 Equipment

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

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

Each echocardiographer who had not been previously certified for a Zogenix study was required to submit a certification ECHO. The certification ECHO was performed on a non-study participant. The participating ECHO facility was informed during the training session that they would not be able to perform ECHOs on true study subjects until they received a "passed" Certification ECHO Evaluation Form. Previously certified echocardiographers were exempt.

3.2.2 Transfer of Echocardiograms

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

3.2.3 Collection of Echocardiograms

ECHOs in Part 2 were taken on Study Day 1, Months 1, 3, 6, 9, 12 (EOS/ET), and 3 and 6 months follow-up for Cohort A; and on Study Day 1, Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, and 72 (EOS/ET), and 3 and 6 months follow-up for Cohort B.

The time of the ECHO was not controlled.

3.2.4 Definition of Baseline

The OLE Baseline value in Part 2 is defined as the last ECHO assessment on or before the first dose in the open-label period. In most cases, this will be the value obtained at Visit 15. Unscheduled assessments prior to First Dose Date in Part 2 will be considered for selection of the baseline values.

The pre-ZX008 Baseline (Core Baseline) is defined as the last ECHO assessment on or before the first dose in Part 1.

3.2.5 Variables Measured

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

In addition to assessing each valve (Mitral, Aortic, Tricuspid, and Pulmonary) for regurgitation PASP was measured or calculated on each ECHO for pulmonary hypertension.

3.2.6 Clinical Analysis of ECHOs

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

- Aortic valve findings were not identical
- Mitral valve findings were not identical
- Left Ventricular Fractional Shortening difference between the two physicians was > 5%
- Left Ventricular Ejection Fraction difference between the two physicians was > 10%
- PASP difference between the two physicians was >10 mmHg
- Clinical significance of the comparison to previous echo's between the two readers was not identical

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

3.2.7 Alert Criteria

Echocardiographic alert criteria included:

- ≥ Mild valve regurgitation (aortic or mitral)
- ≥ moderate valve regurgitation (tricuspid or pulmonic)
- Mean mitral valve gradient ≥ 4 mmHg
- Mean aortic valve gradient ≥ 15 mmHg
- Mean tricuspid valve gradient ≥ 4 mmHg
- Peak pulmonic valve gradient ≥ 21 mmHg
- Tricuspid regurgitation jet velocity > 2.8 meters/sec with or without the findings OR
- One of the following findings in the absence of being able to measure tricuspid regurgitation jet velocity:
    - Change in right ventricle/left ventricle basal diameter ratio > 1.0
    - Right ventricular outflow tract flow acceleration time < 100 ms
    - Dilation of the inferior cava vein (diameter > 21mm and < 50% inspiratory collapse) and/or right atrial dilatation
    - Change in the geometry of the interventricular septum in systole (flattening) with left ventricular eccentricity index > 1.1 in systole and/or in diastole
    - Early diastolic pulmonary regurgitation velocity > 2.2 m/sec
    - Tricuspid Annular Plane Systolic Excursion below 18 mm or below Z-score – 2

4. Statistical Analysis

The statistical analyses of the cardiac safety data are designed to assess the potential cardiotoxicity of ZX008 when administered for an open-label and long term as adjunctive treatment for children and adults with LGS.

4.1 General Principles and Considerations

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

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

ECG and ECHO variables at each time point will be obtained. Changes from OLE baseline will be calculated for each time point after Study Day 1 in Part 2.

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

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

All dates will be displayed in YYYY-MM-DD format (e.g.,2012-12-05).

All analyses will be carried out using SAS® Version 9.4 or higher.

Part 2 summaries will be presented by the subject's Part 1 treatment group (Placebo, ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day)and overall for each time point in Part 2 and the pre-ZX008 Baseline (Core Baseline). The summaries will be presented for each cohort separately.

Data from Part 2, Cohort A will be analyzed after all Cohort A subjects have completed Part 2 or have transitioned to another study. Data from Part 2, Cohort B will be analyzed independently after the last subject in Cohort B completes Part 2. Analysis results for Part 2 from Cohort A and B will be compared through descriptive statistics and if reasonable, some analyses may be performed using data from Cohorts A and B combined.

4.2 Analysis Population

ECG and ECHO data will be analyzed using an OLE Safety Population for each cohort separately, including all subjects who received at least one dose of study medication during the open label extension. The analyses will be based on the actual treatment taken in Part 1.

No comparisons between treatments and sites will be conducted.

4.2.1 Handling of Missing Data

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

4.3 Interim Analysis

4.3.1 Cohort A Interim Analysis for US, Europe Regulatory Submission

COVID-related issues and precautions have delayed the completion of ZX008-1601 Part 2 Cohort A since many subjects have either been unable or unwilling to complete their final visit, and travel restrictions have impeded monitoring visits. Given the uncertainty in predicting when the trial can be completed, an interim analysis of Part 2, Cohort A will be performed to generate the cardiovascular analyses needed to support regulatory submissions to expand the indication for ZX008 in the US and Europe to include the treatment of LGS. This interim analysis will be based on a snapshot of the Cohort A data taken on 19 October 2020 – a date chosen to ensure that the analysis includes at least 365 ± 4 days of exposure in Part 2 for greater than 90% of subjects in Cohort A. The analysis will address all the endpoints in this SAP and will comprise all the outputs listed in Section 5 where the table, figure, or listing number ends in ".1".

4.3.2 Cohort B Interim Analysis for Japan Regulatory Submission

An interim analysis of Part 2 Cohort B cardiovascular data will be performed to support a Partial Change Application (PCA) to expand the indication for ZX008 in Japan to include the treatment of LGS. The interim analysis will be based on a snapshot of the clinical database taken on 09 September 2022 – a date chosen to ensure that the analysis includes at least 365 ± 4 days of exposure in Part 2 for all subjects in Cohort B. The analysis will address all the endpoints in this SAP and will comprise all the outputs listed in Section5 where the table, figure, or listing number ends in ".2".

4.3.3 Final Analysis

A final analysis will be conducted after the last subject in both Cohorts A and B has exited the trial.

4.4 Multiplicity Adjustments

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

4.5 Primary Analyses

4.5.1 Echocardiogram

The number and percentage of subjects with each category of valvular regurgitation will be calculated overall and by Part 1 treatment group by visit for each valve (Mitral, Aortic, Tricuspid, and Pulmonary), based on age (<18 years of age and ≥ 18 years of age), based on mean daily dose (< median and ≥ median),and for all subjects.

PASP will be analyzed for mean, mean maximum change from baseline at each time point, as well as changes in PASP compared to baseline using 5, 10, 15 and 20 mmHg differences. Abnormal values will be categorized by regimen and visit.

4.5.2 Electrocardiogram

The primary analysis of the QTcF is the mean change from baseline (ΔQTcF) at each time point. The upper bound of the one-sided 95% CI (or, equivalently, two-sided 90% CI) of the mean ΔQTcF will be calculated for each time point.

4.6 Secondary Analyses

Central tendency analyses will be conducted to include per-visit data and changes from baseline for the ECG and ECHO values for all subjects. The variables for analysis are listed in sections 2.3.1.2 and 2.3.2.2.

4.7 Additional Analysis

4.7.1 COVID-19 Related Analyses

Additional exploratory table will be constructed to assess the potential impact of COVID-19 on the completion and timing of ECHO assessments. The analyses make the assumption that any visit that occurs after 01 March 2020 – referred to as the COVID-19 period – could be affected by restrictions or changes in behavior related to COVID-19. One analysis will tally the number of subjects who missed ECHO assessments or had assessments out-of-window. The number of out-of-window and missed assessments will also be presented. Another analysis will describe the summary statistics and frequencies of duration between ECHO assessments during the COVID-19 period. A listing of ECHO data collected during the COVID-19 period will also be presented.

4.7.2 Other Additional Analyses

Additional analysis may be used, as appropriate.

4.8 Categorical Analysis

Categorical data will be reported as both numbers and percentages and will include changes from baseline in both ECG and ECHO variables as detailed in section 2.3.

5. Tables, Figures, and Listings

6. References

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REVISION HISTORY

Version	Date Effective	Originator	Comments
0.1	31JUL2020	ERT	First drafted SAP by ERT.
1.0	25AUG2020	ERT	Incorporated review comments from Zogenix.
2.0	22FEB2023	ERT	Incorporated review comments from Zogenix.