16.1.9 Documentation of Statistical Methods

The document listed below is provided in this section.

Statistical Analysis Plan (Protocol ZX008-1601) Version 2.0 dated 08-January-2020

Statistical Analysis Plan for Cardiovascular Endpoints (Protocol ZX008-1601) Version 1.1 dated 23-January-2020

Statistical Analysis Plan (Protocol ZX008-1601) Addendum Note to File dated 31-June-2021

Statistical Analysis Plan

Document Type:	Template	Document ID:	03.007A.03
Issue Date:	02 MAY 2016	Effective Date:	30 MAY 2016

Sponsor Name:	**Zogenix International Limited**
Protocol Number and Title:	ZX008-1601: 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:	**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)**
Syneos Health Project Code:	**1009529A**
Author(s):	[redacted] *Principal Biostatistician*
SAP Version:	2.0
SAP Version Date:	08-Jan-2020

Notice of Confidential and Proprietary Information:

Revision History

Version #	Date (dd-mmm-yyyy)	Document Owner	Revision Summary
0.1	08-Feb-2019	[redacted]	Initial Release Version
0.2	24-May-2019		Separating Part 1 SAP from Part 2 SAP. Requested revisions from Draft 1.
0.3	20-Jun-2019		Separation of Part 1 analyses into Cohort A and Cohort B.
0.4	08-Jul-2019		4th Draft.
0.5	29-Jul-2019		Finalization Version 1.0
1.0	05-Aug-2019		Finalization Version 1.0
1.1	20-Dec-2019		Updates to the Additional Secondary Objectives specified for Part 1, Cohort A in the protocol, and to the associated Additional Secondary Efficacy Endpoints
2.0	06-Jan-2020		Finalization of SAP shells
2.0	08-Jan-2020		Signoff

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

APPROVALS	
Syneos Health	
[redacted]	10-JAN-2020
Lead Biostatistician [redacted]	Date (dd-Mmm-yyyy)
[redacted] Principal Biostatistician [redacted]	10 Jan 2020
Senior Reviewing Biostatistician [redacted]	Date (dd-Mmm-yyyy)
Zogenix International Limited	
[redacted]	Jan-10-2020
	Date (dd-Mmm-yyyy)
[redacted]	09-JAN-2020
[redacted] Statistician on Behalf of Zogenix International Limited	Date (dd-Mmm-yyyy)

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	adverse events
AED	Antiepileptic Drugs
AESI	adverse event of special interest
ALB	albumin
ALT;SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
AS	atonic seizures
AST; SGOT	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BRI	Behavioral Regulation Index
BRIEF	Behavior Rating Inventory of Executive Function
BUN	blood urea nitrogen
Ca	calcium
CBD	cannabidiol
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
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

Abbreviation	Description
GEC	Global Executive Composite
GGT	gamma-glutamyl transferase
GH	Growth hormone
GTC	generalized tonic-clonic seizures
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 Population
MS	myoclonic seizures
MS	myoclonic seizures
Na	sodium
PBPK	physiologically-based pharmacokinetic
PK	pharmacokinetics
PP	Per Protocol Population
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

Abbreviation	Description
SD	standard deviation
SE	status epilepticus
SE	status epilepticus
SOC	System Organ Class
SOP	Standard Operating Procedures
STC	secondarily tonic-clonic
T+M	Titration and Maintenance Periods
T+M	Titration and Maintenance Periods
TA	tonic/atonic seizures
TEAE	Treatment-emergent adverse events
TLF	tables, data listings, figures
TS	tonic seizures
TSH	thyroid stimulating hormone
VABS	Vineland Adaptive Behavior Scale
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 1 of the trial, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

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 pharmacokinetics (PK), electrocardiogram (ECG), and echocardiogram (ECHO).

Separate analysis plans for PK and for ECG/ECHO will be produced.

BioMedical Systems, a division of Biomedical System/ERT, will provide analyses of electrocardiogram (ECG) and echocardiogram (ECHO) data.

2.2. TIMING 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 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.

All objectives will be evaluated in Cohort A and B independently. Data from Part 1, Cohort A will constitute the primary analyses of the study. The primary analyses for Part 1, Cohort A of the study, to include safety, efficacy, and pharmacokinetics, will be conducted once all Cohort A subjects have completed Part 1 of the study and the per-protocol population and other populations have been defined, and approval for unblinding has been granted by Zogenix International Limited. This analysis will be completed by the primary unblinded statistical team of Syneos Health.

Data from Part 1, Cohort B will be analyzed independently after the last subject in Cohort B completes Part 2 and the per-protocol population and other populations have been defined, and approval for unblinding of Cohort B has been granted by Zogenix International Limited.

Analysis results for Part 1 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.

Additional analyses for long-term safety and effectiveness will be completed independently by Cohort once all subjects from each cohort have completed Part 2 of the study. The description of methodology of analysis for Part 2 of the study will be provided in a separate SAP.

2.3. UNBLINDING PLAN

Cohort A is expected to finish Part 1 before Cohort 2. In order to prevent any bias in the completion of Cohort B, whether intentional or unintentional, an unblinding plan will be generated. The unblinding plan will identify individuals (by name or role) who will be unblinded and responsible for the analyses and reporting of Cohort A, Part 1. These unblinded individuals will have no involvement in study decisions that would have the potential to affect data integrity for Cohort B.

3. PART 1 OBJECTIVES

Cohorts A and B will be analyzed independently. Cohort A will be analyzed after the last subject completes Part 1. These analyses will form the main analyses to establish safety and efficacy of ZX008 in patients with LGS. Cohort A Part 1 will be evaluated with formal statistical testing as described below. Cohort B will be analyzed after the last subject completes Part 2. Inferential statistics for Cohort B will be evaluated using the same methodology stated for Cohort A, but the inferential statistics will be considered as descriptive.

3.1. PRIMARY OBJECTIVE

The primary objective of Part 1, Cohort A is the primary objective of the entire study. The primary objective of Part 1 is:

- To evaluate the effect of ZX008 0.8 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with Lennox-Gastaut syndrome (LGS) based on the change in frequency of seizures that result in drops (DSF) between baseline and the combined Titration and Maintenance Periods (T+M).

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].

3.2. KEY SECONDARY OBJECTIVE

The key secondary objectives of Part 1, Cohort A are:

- To evaluate the effect of ZX008 0.2 mg/kg/day versus placebo as adjunctive therapy for the treatment of uncontrolled seizures in children and adults with

LGS based on the change in DSF baseline and Titration and Maintenance Periods (T+M).

- To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the proportion of subjects who achieve a ≥ 50% reduction from baseline in the frequency of seizures that result in drops.
- To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the principal investigator.

3.3. ADDITIONAL SECONDARY OBJECTIVES

Additional secondary objectives of Part 1, Cohort A of the study are:

- To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the following endpoints:
  - Change in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) between baseline and the combined T+M whether ESC confirmed as drop or not.
  - Change in the frequency of all countable motor seizures between baseline and T+M (countable seizures include: GTC, SGTC, TS, AS, TA, clonic seizures [CS], focal seizures with clear observable motor signs [FS], and hemiclonic seizures [HS]).
  - Change in the frequency of all countable non-motor seizures between baseline and T+M (countable non-motor seizures include: absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms)
  - Change in the frequency of all countable seizures (i.e., motor and non-motor) between baseline and T+M
  - Change in frequency of seizures that result in drops (ESC confirmed) between baseline and the Maintenance Period (M)
  - Change in frequency of seizures that (typically) result in drops between baseline and the Maintenance Period (M)
  - Change in the frequency of all countable motor seizures between baseline and M
  - Change in the frequency of all countable non-motor seizures between baseline and M
  - Change in the frequency of all countable seizures (i.e., motor and non-motor) between baseline and M
  - The proportion of subjects who achieve a worsening, >0 - <25%, ≥25%, ≥50%, ≥75%, 100% reduction, and “near seizure freedom” (i.e. 0 or 1 seizures) between baseline and T+M, and baseline and M, in 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) 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)

- To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the parent/caregiver.

3.4. SAFETY OBJECTIVES

The safety objectives of Part 1, Cohort A are:

- To evaluate the safety and tolerability of ZX008 0.2 and 0.8 mg/kg/day versus placebo with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, vital signs (blood pressure, heart rate, temperature, and respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), body weight, and body mass index (BMI)
- To evaluate the change from baseline in cognition using age-appropriate versions of the Behavior Rating Inventory of Executive Function (BRIEF)

3.5. PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objective of the study is:

- To evaluate the PK of ZX008 0.2 and 0.8 mg/kg/day at steady state in subjects < 18 years and ≥18 years with LGS using a non-compartmental analysis and obtain exposure data that will be used in population pharmacokinetic (PopPK) analysis, the results of which will be reported separately.

3.6. EXPLORATORY OBJECTIVES

The exploratory objectives of the study are:

- To compare the ZX008 0.2 and 0.8 mg/kg/day doses on primary, secondary, and safety endpoints.
- To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the following endpoints:
  - The change from baseline in behavior using the Vineland Adaptive Behavior Scale (VABS)
  - The change from baseline in quality of life (QoL) using the QOLCE
  - The change from baseline in caregiver burden using the Zarit Caregiver Burden Inventory
  - The change from baseline in affective symptoms of the parent/caregiver using the Hospital Anxiety and Depression Scale (HADS)
  - The frequency of rescue medication usage
  - The incidence of medical services to treat seizures
  - The incidence of status epilepticus.

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. The primary analysis will be conducted when the last subject in Cohort A has completed Part 1. Part 2 will be an open-label, flexible-dose extension for subjects completing Part 1 of 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 consists of the 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 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-ups at 3 and 6 months. Subjects enrolled in Germany, France and Netherlands will have an additional follow-up at 24 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) 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.

A follow-up ECG and ECHO will be performed at 3 and 6 months after study drug discontinuation for early termination and for those subjects who complete Part 2. Subjects enrolled in Germany, France and Netherlands will have an additional follow-up at 24 months. If there are any findings at a post-dose follow-up, another follow-up will 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.

4.1. SUBJECT SELECTION

The inclusion and exclusion criteria are stated in full in the protocol document in sections 4.1, 4.2, and 4.3.

4.2. DETERMINATION OF SAMPLE SIZE

The sample size for Part 1 Cohort A was estimated under the assumption that adding ZX008 at 0.8 mg/kg/day to current therapy will lead to a mean decrease in drop seizures that is 30 percentage points greater than adding placebo to current therapy. For example, if adding placebo leads to a 10% decrease in seizures, then adding the high dose of ZX008 would be expected to decrease seizures by at least 40%.
The variability expected in the trial was estimated from a Phase 3 trial of clobazam for patients with Lennox-Gastaut syndrome (Ng 2011) leading to an assumption that the standard deviation (SD) is 50%. Other assumptions include an allowance for 20% dropouts between randomization and the start of the maintenance period. Under these assumptions, a sample size of 63 subjects per treatment group for a nonparametric analysis affords 90% power to detect a difference between the ZX008 0.8 mg/kg/day and placebo groups that is significant at the α=0.05 level. Assuming a 20% drop-out rate prior to the start of the maintenance period yields a requirement for an additional 14 subjects per group for a total of 79 subjects per treatment group for a nonparametric analysis. Similar calculations for the 0.2 mg/kg/day ZX008 group lead to a total required

sample size of 237. The number of subjects randomized into Part 1 Cohort A is estimated to be approximately 250 due to the long baseline period.

4.3. TREATMENT ASSIGNMENT & BLINDING

Upon completion of the Baseline Period in Part 1, subjects who qualified for the study were randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; 30mg/day maximum [0.2 mg/kg/day or 0.5 mg/kg/day; 20 mg/day maximum for subjects taking concomitant STP]) or placebo. The randomization was stratified by weight (<37.5 kg, ≥37.5 kg) to ensure balance across treatment arms, with a target of at least 25% in each weight group. Subjects were assigned a randomization number by the IWR system upon confirmation that the subject qualified for enrollment in the Titration Period.

The primary biostatistical team, data management team, and clinical team will remain blinded to subject treatment assignments until approval is given for the unblinding of the Part 1, Cohort A database and finalization of inclusion in the study populations is made.

The release of unblinded pharmacokinetic concentration data, ECG and ECHO data to facilitate external analyses will be completed only after the approval for unblinding of the Part 1 database by Zogenix.

4.4. ADMINISTRATION OF STUDY MEDICATION

Each bottle of study medication contains the appropriate concentration and volume of liquid to administer the assigned treatment (ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day [or 0.5 mg/kg/day for subjects taking concomitant STP], or placebo). ZX008 and placebo are identical, thus rendering the study drug and placebo indistinguishable.

The blinding scheme instituted for this study ensures that the volume of study medication taken cannot be associated with the dose group, thus unblinding the study. This is achieved by random assignment of different concentrations of ZX008 or placebo (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the IWR system. The IWR system instructs site personnel to the volume of oral solution to be administered based on that subject's weight. (Dose is recalculated by the system based on weight once at the midpoint of Part 1 of the study.) During the Titration, Maintenance, and Taper/Transition Periods, the subjects and study personnel (investigators, clinical staff, personnel involved in data collection and analysis, the Medical Monitor, and the sponsor) are blinded to the treatment allocation and to the concentration of ZX008. If an investigator feels the blind should be broken, he/she can do so when necessary for treatment decisions. However, the investigator should endeavor to discuss with the Medical Monitor or Sponsor's Medical Representative, if available. The blind should only be broken in the event the knowledge of whether the subject is on active study medication versus placebo is needed to determine course of medical treatment for the event. The subject will be discontinued from the clinical trial upon breaking of the blind

and the decision whether the subject can enter Part 2 will rest with the Sponsor if the subject exited Part 1 prior to completion.

Following randomization subjects enter the Titration Period and are blindly titrated to their randomized dose as outlined in Table 1.

Table 1: Titration Algorithm for Part 1

Randomized Group	Titration Step 1 Study Days 1-4	Titration Step 2 Study Days 5-8	Titration Step 3 Study Days 9-14
ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day (0.5 mg/kg/day for subjects taking concomitant STP)	ZX008 0.2 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.8 mg/kg/day (0.5 mg/kg/day for subjects taking concomitant STP)
Placebo	Placebo	Placebo	Placebo

After completion of the Titration Period, subjects enter the Maintenance Period and continue to receive the randomized dose of ZX008 or placebo and be treated for an additional 12 weeks.

Subjects who complete the Maintenance Period and do not be continue into Part 2, the open-label extension, and subjects who discontinue from Part 1 early, will be tapered off of study medication as outlined in Table 2.

Table 2: Taper Algorithm for Part 1

Randomized Group	Taper Step 1 Day 1-4 after study completion or early termination	Taper Step 2 Days 5-8 after study completion or early termination
ZX008 0.2 mg/kg/day	Placebo	Placebo
ZX008 0.8 mg/kg/day (0.5 mg/kg/day for subjects taking concomitant STP)	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
Placebo	Placebo	Placebo

Subjects who complete the Maintenance Period and will be continuing into the open-label extension (Part 2) will be transitioned from double-blind study medication to open-label ZX008. All subjects entering the open-label extension (Part 2) will be transitioned from their blinded daily dose to the 0.2 mg/kg/day dose during the 2-week interval between Visits 12 and 15, without breaking the blind. The IWR system will assign two bottles of Investigational Medicinal Product (IMP) to the subject, one for

each step in the transition. A new bottle of IMP will be started by the subject at each level of the transition step.

Table 3: Transition Algorithm for Part 1

Dose Group in Double-Blind Study	Transition Step 1 Day 1-4 after Visit 12	Transition Step 2 Day 5-14 after Visit 12
ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day (0.5 mg/kg/day for subjects taking concomitant STP)	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
Placebo	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day

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

Table 4 – Schedule of Assessments

Part 1 Assessments

Study Assessments – PART 1	**Baseline Period[a]**			**Titration + Maintenance Period**								**EOS/ ET[b]**	**Post-Dosing[l]**	**Cardiac Follow-up[c]**
Visit Number	**Screening**	**2** (Phone)	**Random-ization**	**Titration Period**			**Maintenance Period**							
	1		**3**		**4, 5** (Phone)	**6**	**7** (Phone)	**8**	**9** (Phone)	**10**	**11** (Phone)	**12**	**13**	**14**
Study Day	**-28**	**-15**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**197**
Informed Consent (subject and parent/caregiver)	X											X (Part 2)		
Inclusion/Exclusion Criteria	X		X											
Demographics	X													
Medical/Neurological History	X													
Epilepsy history	X													
Review retrospective seizure diary data	X													
Prior Medication, including AEDs	X		X											
Physical Examination, complete	X		X									X		Optional
Physical Examination, abbreviated						X[m]		X[m]		X[m]				X
Neurological Examination, complete	X											X		
Neurological Examination, abbreviated			X			X[m]		X[m]		X[m]				
Vital signs	X		X			X		X		X		X		
Weight	X		X			X		X		X		X		

Table 4 – Schedule of Assessments

Part 1 Assessments

Study Assessments – PART 1	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Post-Dosing[l]	Cardiac Follow-up[c]
Visit Number	Screening		Random-ization	Titration Period			Maintenance Period							
	1	2 (Phone)	3		4, 5 (Phone)	6	7 (Phone)	8	9 (Phone)	10	11 (Phone)	12	13	14
Study Day	**-28**	**-15**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**197**
Height	X											X		
Chest x-ray (France, Netherlands only)			X									X		X
12-lead ECG	X		X					X				X		X
Doppler ECHO	X							X[d]				X[d]		X
Urine or Serum Pregnancy Test	X[e]		X[e]					X[e]				X[e]		
Clinical laboratory evaluation (hematology/ chemistry/urinalysis[o], etc)	X		X					X				X		
Plasma sample for ZX008 PK								X[f]						
Plasma sample for background AEDs PK			X[g]			X[g]		X		X[g]		X[g]		
Whole blood CBD/ THC Panel	X		X					X				X		
Tanner Staging (for subjects >7 to 18 years old)			X									X		
Subject Diary	D	R	C/R/D		R	C/R/D	R	C/R/D	R	C/R/D	R	C/R/D[h]	C/R	
Epilepsy genotype panel (optional)	X													
Study Medication			D		R[i]	C/R/D	R	C/R/D	R	C/R/D	R	C/R/D[h]	C/R	
C-SSRS	X		X			X		X		X		X		

Table 4 – Schedule of Assessments

Part 1 Assessments

Study Assessments – PART 1	**Baseline Period[a]**			**Titration + Maintenance Period**								**EOS/ ET[b]**	**Post-Dosing[l]**	**Cardiac Follow-up[c]**
Visit Number	**Screening**		**Random-ization**	**Titration Period**			**Maintenance Period**							
	1	**2 (Phone)**	**3**		**4, 5 (Phone)**	**6**	**7 (Phone)**	**8**	**9 (Phone)**	**10**	**11 (Phone)**	**12**	**13**	**14**
Study Day	**-28**	**-15**	**-1**	**1**	**4, 8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**197**
Clinical Global Impression - Improvement (assessed by parent/caregiver)						X		X		X		X		
Clinical Global Impression - Improvement (assessed by Principal Investigator)						X		X		X		X		
HADS (Effect of parent/caregiver)			X									X		
BRIEF			X									X		
VABS			X					X				X		
QOLCE			X									X		
Zarit Burden			X					X				X		
Randomize subject			X[n]											
First Day of Study Drug Administration[j]				X[j]										
Daily Diary Completion							X							
Concomitant Medication								X						
Adverse events							X							
Adverse events of special interest							X							X[k]

Table 4 – Schedule of Assessments

Part 1 Assessments

Study Assessments – PART 1	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Post-Dosing[l]	Cardiac Follow-up[c]
Visit Number	Screening	2 (Phone)	Random-ization	Titration Period			Maintenance Period							
	1		3		4, 5 (Phone)	6	7 (Phone)	8	9 (Phone)	10	11 (Phone)	12	13	14
Study Day	-28	-15	-1	1	4, 8	15	29	43	57	71	85	99	113	197

Abbreviations: AED=antiepileptic drug; BMI=body mass index; C=Collect; CBD=cannabidiol; D=Dispense; ECG=electrocardiogram; EQ-5D-5L=standardized measure of health status; EOS=end of study; ET=early termination; HADS=Hospital Anxiety and Depression Scale; BRIEF=Behavior Rating Inventory of Executive Function; QoL=quality of life; R=Review; VABS=Vineland Adaptive Behavior Scale

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

b: Subjects who are discontinued early and those who complete the study and choose not to enroll in the separate open-label extension will be tapered off study medication over an up to 2-week period.

c: The safety follow-up visit will be conducted for subjects who either terminate early from Part 1, or who complete Part 1 but do not enter 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 the last post-dose follow-up, a follow-up visit will be repeated every 3 months until resolved or stabilized.

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

e: Females of child-bearing potential

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

g: Plasma sample for assessment of background AED(s) will be conducted prior to the dose of AED(s) at Visits 3, 8 and 12 (Visits 6 and 10 only if clinically indicated). AED plasma sample may be collected after the morning dose of AEDs are taken, if preferable, as long as the time of last dose is accurately recorded.

h: Study drug/diary dispensed for the Transition Period for subjects entering the open-label extension and for the Taper Period for subjects exiting the study.

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

j: Study drug administration begins in the morning of Study Day 1. Study Day 1 is considered the first day of dosing, even though subjects may receive an in-clinic dose on Study Day -1. If the first dose is taken in the clinic, it will be recorded in the eCRF, but not the subject diary; the next dose on the morning of Study Day 1 will be the first entry in the subject's diary.

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

l: Visit 13 may be conducted as a phone call, provided diaries and study medication are returned by this time.

m: An abbreviated physical and/or neurological examination to be conducted as appropriate based on last exam and reported AEs.

n: Randomization should not occur prior to receiving approval from the Epilepsy Study Consortium and ERT ECHO results.

Table 4 – Schedule of Assessments

Part 1 Assessments

Study Assessments – PART 1	Baseline Period[a]			Titration + Maintenance Period								EOS/ ET[b]	Post-Dosing[l]	Cardiac Follow-up[c]
Visit Number	Screening	2 (Phone)	Random-ization	Titration Period			Maintenance Period							
	1		3		4, 5 (Phone)	6	7 (Phone)	8	9 (Phone)	10	11 (Phone)	12	13	14
Study Day	-28	-15	-1	1	4, 8	15	29	43	57	71	85	99	113	197

o: 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.

The targeted study day and allowable windows for visits in Part 1 are reproduced from the protocol below. Early termination visits will be mapped to a visit based on these windows.

Table 5: Visit windows for Part 1 Visits

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Clinic; Study Day -29 to -28 or -28 to -27):	Not Applicable
Visit 2 (Phone; Study -15)	± 3 days
Visit 3 (Clinic; Study Day -1; Randomization	± 4 days [a]
Visits 4, 5 (Phone: Study Days 4, 8)	± 3 days
Visit 6 (Clinic; Study Day 15)	± 4 days
Visit 7 (Phone; Study Day 29)	± 4 days
Visit 8 (Clinic; Study Day 43)	± 4 days
Visit 9 (Phone: Study Day 57)	± 4 days
Visit 10 (Clinic; Study Day 71)	± 4 days
Visit 11 (Phone: Study Day 85)	± 4 days
Visit 12 (Clinic: Study Day 99)	± 4 days
Visit 13 (Clinic; Study Day 113; post dosing)	± 4 days
Visit 14 (ECHO clinic; 3-24 months after last dose)[b]	+ 30 days

AED=antiepileptic drug (s); ECHO=echocardiogram;.
[a] In cases where the screening period is extended beyond 28 days, the immediate 28 days before the Randomization visit will be used to calculate the baseline seizure frequency
[b] All subjects are required to have follow-ups at 3 and 6 months post-treatment. Subjects enrolled in Germany, France and Netherlands will have an additional 24-month follow-up.

5. ENDPOINTS

5.1. PRIMARY EFFICACY ENDPOINT

Percent change from baseline in the frequency of seizures that result in drops (DSF) in the combined Titration and Maintenance Periods (T+M) in the ZX008 0.8 mg/kg/day group compared to the placebo group. Seizures that results in drops are GTC, SGTC, TS, AS, and TA confirmed for each subject as a drop seizure by the ESC.

5.2. KEY SECONDARY EFFICACY ENDPOINTS

The key secondary endpoints are:

- Change from baseline in DSF in T+M in the ZX008 0.2 mg/kg/day group compared to the placebo group.
- Proportion of subjects who achieve a ≥50% reduction from baseline in the frequency of seizures that result in drops comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.
- Proportion of subjects who achieve improvement (minimally, much or very much improved) in the Clinical Global Impression – Improvement as assessed by the Principal Investigator comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.

5.3. ADDITIONAL SECONDARY EFFICACY ENDPOINTS

The additional secondary endpoints are:

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

- Change from baseline during T+M in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) whether ESC confirmed as drop or not.
- Change from baseline during T+M in frequency of all countable motor seizures (GTC, SGTC, TS, AS, TA, CS, FS, and HS).
- Change from baseline during T+M in frequency of all countable non-motor seizures (absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms).
- Change from baseline during T+M in the frequency of all countable seizures (i.e., motor and non-motor).
- Change from baseline during M in the frequency of seizures that result in drops.
- Change from baseline during M in the frequency of seizures that typically result in drops.
- Change from baseline during M in the frequency of all countable motor seizures.
- Change from baseline during M in the frequency of all countable non-motor seizures.
- Change from baseline during M in the frequency of all countable seizures (i.e., motor and non-motor).
- Proportion of subjects who achieve a worsening from baseline (i.e. ≤ 0% reduction), or >0%, ≥25%, ≥50%, ≥75%, or 100% reduction between baseline and T+M, and baseline and M, in 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 in the baseline, M and T+M period, defined as 1) days with no seizures that results in drops (ESC confirmed), and 2) days with no countable motor seizures
- The longest interval (days) between seizures that result in drops (ESC confirmed) comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo

- Clinical Global Impression – Improvement as assessed by the parent/caregiver

5.4. SAFETY ENDPOINTS

The safety endpoints for Part 1 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)

5.5. EXPLORATORY ENDPOINTS

The exploratory endpoints for Part 1 of the study are:

- The change from baseline in behavior using the Vineland Adaptive Behavior Scale (VABS)
- The change from baseline in quality of life (QoL) using the Quality of Life in Childhood Epilepsy (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
- Incidence of status epilepticus in the M and T+M period.
- Incidence of rescue medication usage in the T+M and M periods
- Number of days rescue medication used in the T+M and M periods
- Incidence in use of medical services to treat seizures in the M and T+M periods

6. 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.

6.1. ENROLLED POPULATION

The enrolled population is defined as all subjects who signed the informed consent form. This population will be used for listings.

6.2. SAFETY (SAF) POPULATION

All Part 1 safety analyses will be performed on the SAF Population defined as all randomized subjects who receive at least one dose of ZX008 or placebo.

6.3. MODIFIED INTENT-TO-TREAT (MITT) POPULATION

The mITT Population is defined as all randomized subjects who receive at least one dose of ZX008 or placebo and for whom at least one week of diary data are available. Subjects will be analyzed according to the treatment group to which they were randomized. The primary comparison of ZX008 0.8 mg/kg/day to placebo, as well as key secondary analyses, will be performed on the mITT Population.

6.4. PER PROTOCOL (PP) POPULATION

The PP Population is defined as all randomized subjects who receive at least one dose of ZX008 or placebo, who complete at least 4 weeks of diary data in the maintenance period, and who have no major protocol deviations that would have a significant impact on clinical outcome of Part 1 data, and who have met the inclusion criteria for baseline drop seizure count. Protocol deviations that occurred during Part 1 will be reviewed and the list of deviations warranting exclusion from the PP Population will be finalized prior to study unblinding.

6.5. PROTOCOL DEVIATIONS

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

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

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

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

Deviations will be reviewed prior to the database lock of Part 1 data to determine which deviations will be classified as leading to exclusion from the PP set.

6.6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.6.1. General Methods

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

Part 1 summaries will be presented by treatment group (Placebo, ZX008 0.2 mg/kg/day, ZX008 0.8 mg/kg/day).

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

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

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

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

6.6.2. Definitions

First Dose Date: First Dose Date of Investigational Drug: If the first diary date on the day after randomization indicates that investigational drug was taken on this day, then the first dose date will be the date after randomization (Study Day 1). In all other situations where it is known that the subject took at least one dose of medication, the first dose date will be assumed to be 1 day after the date of randomization.

Study Day: Study day will be calculated relative to the First Dose Date in the Titration Period. 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.

Baseline Value: For non-seizure frequency assessments, the Part 1 baseline value will be the last non-missing assessment collected on or prior to the first date of dosing in Part 1. Unscheduled assessments prior to First Dose Date will be considered for selection of the baseline value. 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) using methods described below.

6.6.3. 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, 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.

	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 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 AE end day is missing but month and year are present then Impute the last day of the month unless month is same as month of last dose of study drug then impute last dose date. Missing day and month – If AE has missing day and month but year is present then impute 31st December unless year is the same as first dose date then impute last dose date. Completely Missing – need to look at whether the AE is still ongoing before imputing a date and also when it started in relation to study drug. If the ongoing flag is missing then assume that AE is still present

	(i.e. do not impute a date). If the AE has stopped and start date is prior to first dose date then impute the 1st dose date. If 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). On each day, subjects are asked a question of whether there is a seizure to report that day. Subjects may either answer "Yes" and continue to complete more details about the seizure, or answer "No, this 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 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 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 and it is indicated that there were seizures that day, that day will be considered to have missing diary data.

6.7. VISIT WINDOWS

The following rules will be used to window data into treatment periods for by treatment period tabulations. For all by-visit tabulations, the nominal visit as recorded on the electronic Case Report Form (eCRF) will be used.

The following are the definitions for associating dates with the treatment periods of Part 1.

Baseline Period	The Baseline Treatment period will be the 28 days immediately prior to the date of the Study Day 1.
Double Blind Treatment Period	The Double-Blind Treatment Period start date is the date of first full daily dose (i.e. Study Day 1). The Double-Blind Treatment Period end date is the last date the subject was on study treatment in Part 1. The Double-Blind Treatment Period consists of 16 weeks from first treatment start date, which includes 2 weeks of Titration period, 12 weeks of Maintenance period and 2 weeks of Taper/Transition period. The end date for efficacy analyses is the last day of Maintenance treatment, or Visit 12; the end date for safety analyses is the last day of

	Taper/Transition, which would be considered the date at Visit 15. For subjects who discontinue early from the study, the double-blind treatment period end date for efficacy analyses will be the date at the early termination visit (Visit 12); the end date for safety analyses would be the date of Visit 13. If a taper is not conducted, the end date for both analyses would be Visit 12.
Titration Period	The Titration Period begins on the first full day of treatment (Study Day 1) and extends through Visit 6 (when the subject has reached their randomization dose). The Titration Period applies to all subjects including placebo recipients. If a subject withdraws from the study prior to treatment in the maintenance period, all safety assessments and events up to and including the date of study withdrawal will be tabulated in the titration period.
Maintenance Period	The Maintenance Period covers the 12 weeks following the end of the titration period. It begins on the date of Visit 6 + 1 day and extends through the end of study/early termination visit (Visit 12).
Titration + Maintenance Period (T+M)	The T+M period combines the Titration and Maintenance periods, beginning on the date of first treatment (Study Day 1) and extending through the end of study/end of treatment visit (Visit 12).
Taper/Transition Period	The Taper/Transition period consists of 2 weeks starting from end of study/early termination visit (Visit 12) + 1 day through Visit 13 (Taper) or Visit 15 (Transition to Part 2). For subjects who are not entering into the Part 2 of the study, subjects will gradually be tapered off of study medication. For subjects who are entering Part 2, subjects will enter the transition phase where all subjects will be on a dose of 0.2 mg/kg/day at the end of this phase.

6.8. POOLING OF CENTERS

Analysis will be pooled overall and by cohort (A vs. B).

6.9. SUBGROUPS

The following subgroups will be utilized for some efficacy analyses and adverse event summarizations:

Age: 2– <6 years, 6–<12 years, 12 - <18, 2-<18 years, ≥ 18 – 35 years.

Sex: Male, Female

Baseline Weight: <37.5 kg vs. ≥ 37.5 kg

Number of concomitant Antiepileptic Medications Used: ≤2, 3, ≥4 medications

Number of prior Antiepileptic Medications Used: 0-3, 4-6, 7-9, ≥10 medications

Baseline Frequency of Seizures that Result in Drops (events/28 days): based on observed tertiles

Usage of a specific concomitant medication(s) (top 3 concomitant AEDs to be determined by data review) (Yes / No)

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. SUBJECT DISPOSITION AND WITHDRAWALS

The Part 1 subject disposition will be presented per treatment group and overall for Cohort A and B independently.

For describing the Part 1 subject disposition, the following will be summarized by number and percentage:

- Subjects enrolled (only overall)
- Subjects enrolled but not randomized and reason for not-randomized (only overall)
- Subjects randomized
- Subjects in SAF
- Subjects in mITT
- Subjects in PP
- Subjects assigned to SAF, mITT, PP and discontinued the study and reason.
- Number of subjects in the trial per trial period/phase (Titration Phase, Maintenance Phase, Taper Period for those not entering Part 2, and Follow-up Period) will be presented for SAF and mITT sets.
- Trial completers
  - Trial completers continuing into Part 2
  - Trial completers not continuing into Part 2 and reason for not continuing

Part 1 trial completers include: 1.) subjects who did not discontinue prior to the Visit 12, and 2.) subjects who completed at least through Visit 8 and enrolled into the Part 2 open label extension.

For subjects enrolled but not randomized to treatment in Part 1, and for the tallies listed under each reason for not being randomized, the denominator used to calculate the percentage will be the number of enrolled subjects. For all other calculations in the Part 1 disposition table, the denominator will be the number of subjects randomized.

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

7.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Part 1 subject demographics and baseline characteristics will be summarized descriptively per treatment group and overall, for the SAF and mITT populations for Cohort A and B.

The following demographic characteristics will be summarized:

- Age [Years]
- Categorized age as: 2 - <6 years, ≥ 6 - <12 years; ≥12 - <18 years, ≥ 18 – 35 years.
- Sex
- Race
- Ethnicity
- Height [m]
- Weight [kg]
- BMI [kg/m^2]
- Geography: North America, Europe, Australia, Japan (Cohort B analysis only)

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

7.3. MEDICAL HISTORY, NEUROLOGIC HISTORY, AND CONCOMITANT DISEASES

Medical history and neurologic history will be summarized and sorted alphabetically, by primary System Organ Class and Preferred Term coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later. The number and percentage of subjects will be displayed for each System Organ Class (SOC) and Preferred Term (PT) within treatment group.

Medical history will be presented for the SAF population, separated by Cohort A and B.

All medical history data of subjects will be listed for the enrolled population, by Cohort A and B.

7.4. MEDICATION

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

The following algorithm will be used to define prior and concomitant in Part 1.

Prior medications will be those with a stop date prior to first dose administration in Part 1.

Concomitant medications in Part 1 will be defined as those medications that were initiated after study drug administration in Part 1 (but excluding medications that started on or after the first dose of study medication in Part 2) or those medications that were ongoing at the date of first study drug administration in Part 1.

The medication will be assumed to be prior medication if it cannot be definitively shown that the medication did not start or continue during the Part 1 treatment period.

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

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

A medication may be counted as concomitant in Part 1 and in Part 2. By definition, a prior medication cannot be counted as concomitant in Part 1. Medication will be summarized and sorted alphabetically separately for prior and concomitant medication by Anatomical Therapeutic Chemical (ATC) categories (Level 2: pharmacological or therapeutic subgroup and Level 3: chemical or therapeutic or pharmacological subgroup) and WHO-DD drug code. For each medication the number and percentage of subjects will be displayed.

Part 1 medication summary tables will be presented for the SAF population.

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

7.4.1. Prior and Concomitant Antiepileptic Treatments

Medication (collected on the prior antiepileptic medications, prior medications, and concomitant medications eCRF page) will be coded using the World Health Organization Drug Dictionary (WHO-DD) Format B3 Version Sep2017 or later. Anti-epileptic medications will be identified using any drug entered on the prior-antiepileptic medication page and anti-seizure concomitant medications with indication of "Lennox-Gestaut Syndrome".

Prior and concomitant antiepileptic medications will be defined and analyzed for the SAF and OLE similar to concomitant medications as described in Section 7.4.

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

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

8. EFFICACY

The analysis of the Part 1 primary and secondary efficacy parameters will be performed on the mITT population for Cohort A and B independently, except where noted.

The Part 1 primary efficacy endpoint and key secondary efficacy analyses will be repeated on the PP Population for Cohort A and B independently, in order to assess the impact of major protocol deviations on the key inference.

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

8.1. MULTIPLICITY STRATEGY AND TESTING HIERARCHY

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

The hierarchy starts with the primary analysis comparing ZX008 0.8 mg/kg/day to placebo on the change in number of seizures that results in drops from baseline. The next steps in the hierarchy entail the comparisons for the key secondary endpoints.

- Change from baseline in frequency of seizures that result in drops in T+M in the ZX008 0.2 mg/kg/day group compared to placebo.

- Proportion of subjects who achieve a ≥50% reduction from baseline in the frequency of seizures that result in drops in the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.
- Proportion of subjects who achieve improvement (minimally, much, or very much improved) in the Clinical Global Impression – Improvement (CGI-I) as assessed by the Principal Investigator comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.

Below is a complete list of steps in the testing hierarchy in order:

1. Compare ZX008 0.8 mg/kg/day to placebo on the change in frequency in seizures that result in drops per 28 days between the Baseline and T+M periods.
2. Compare ZX008 0.8 mg/kg/day to placebo on the proportion of subjects who achieve a ≥ 50% reduction from baseline in the number of seizures that result in drops.
3. Compare ZX008 0.8 mg/kg/day to placebo on the CGI-I at Visit 12.
4. Compare ZX008 0.2 mg/kg/day to placebo on the change in frequency in seizures that result in drops per 28 days between the Baseline and T+M periods.
5. Compare ZX008 0.2 mg/kg/day to placebo on the proportion of subjects who achieve a ≥ 50% reduction from baseline in the number of seizures that result in drops.
6. Compare ZX008 0.2 mg/kg/day to placebo on the CGI-I at Visit 12

8.2. PRIMARY EFFICACY ENDPOINT AND ANALYSIS

8.2.1. Primary Efficacy Endpoint Definition

The Part 1 primary efficacy endpoint is the percent change from baseline in the frequency in seizures that result in drops per 28 days in the T+M period. 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]

For each subject, the frequency of drop seizures will be calculated from all available data collected during the Baseline and T+M Periods. Subjects in the ZX008 0.8 mg/kg/day treatment group will be compared to those in the placebo on the frequency of drop seizures (DSF) during T+M adjusted for the frequency during Baseline using a non-parametric ANCOVA model.

The baseline period is the 28 days immediately preceding the date of Study Day 1. The T+M period is planned for 14 weeks. However, actual durations will be computed for

each subject based on the individual subject's start and stop dates for each period, except that if the baseline period is longer than 28 days, the frequency for the baseline period will be calculated with data from the 28 days immediately preceding the Study Day 1.

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 frequency of seizure episodes 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 response to the Question 12 for frequency of episodes
A cluster of seizures back to back	This will be determined empirically dependent on the duration of the cluster event and the number of events reported in a discrete seizure event for subjects in the study.

Seizure Clusters

Seizure clusters are entered in the DSD by estimating the duration of the cluster in hours: minutes; seconds. For seizure clusters the number of discrete seizures that occurred during a cluster is not entered in the DSD. In order to estimate the number of seizures during a 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 discrete seizures include both an estimate of the number of seizures, and an estimate of the duration, categorized into 1 of 3 buckets: <2 minutes; 2-10 minutes; >10 minutes.

Study-level summary statistics using seizure events reported in the T+M period will be calculated for each bucket to determine the median number of seizures occurring in each bucket.

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

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

- 'long' clusters (i.e., >5 hours) will be the median number of seizures reported in discrete seizure events >10 minutes.

For any individual subject, the frequency of drop seizures per 28 days during the baseline period (DSF_B) will be derived as follows:

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

For each treatment group, the median and mean DSF_B will be calculated.

Similarly, for each subject, the frequency of DSF per 28 days for the T+M period (DSF_{T+M}) is derived as below:

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

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

$PCDSF_{T+M} = (DSF_{T+M} - DSF_B)*100/DSF_B$

The difference from baseline ($CDSF_{T+M}$) will be estimated by $CDSF_{T+M} = DSF_{T+M} - DSF_B$.

For each treatment group, descriptive statistics for DSF during baseline, T+M and M only, as well as the differences and % changes from baseline, will include the number of observations, mean, standard deviation, median, minimum and maximum, overall.

8.2.2. Part 1 Primary Efficacy Endpoint Analyses

T+M Period:

The primary analysis will compare the ZX008 0.8 mg/kg/day group to the placebo group for Cohort A using a two-sided test at the α=0.05 level of significance.

The primary endpoint will be analyzed using a non-parametric analysis of covariance (ANCOVA) model with treatment group (three levels; Placebo, 0.2 mg/kg/day, 0.8 mg/kg/day) and weight strata group (< 37.5 kg, ≥ 37.5 kg) as factors, rank of baseline DSF_B as a covariate and rank of percent $CDSF_{T+M}$ as response. Treatment group mean differences from placebo will be estimated via least squares means from the analysis model along with 95% confidence intervals.

The null hypothesis

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

will be tested against the alternative

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

where $\mu_{Z0.8}$ and μ_P represent the ZX008 0.8 mg/kg and Placebo group location parameter, respectively.

Rejection of the null hypothesis in favor of the alternative, in the presence of a statistically significantly smaller seizure frequency for the treatment group compared to the placebo group, (two-sided p-value <.05) will be regarded as evidence of a treatment benefit in favor of the 0.8 mg/kg group. A similar comparison of the location parameter ~~for~~ Z008 0.2 mg/kg/day vs. placebo will be regarded as evidence of a treatment benefit of the 0.2 mg/kg group. This is the 3rd key secondary endpoint.

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

```
Proc rank data=temp ties=mean out=ranktemp;
  Var bsrd csrd;
  Rank r_bsrd r_csrd;
Run;
proc glm data=ranktemp;
        class wtgrp trtp;
        model r_csrd = r_bsrd wtgrp trtp  / SS3;
        lsmeans  trtp / pdiff stderr;
```

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

r_bsrd = rank of baseline DSF_B,
r_csrd = rank of percent $CDSF_{T+M}$
wtgrp = weight group.

Additional statements may be used to obtain estimates and associated 95% confidence intervals.

A second analysis of the primary endpoint will be completed using a parametric analysis of covariance (ANCOVA) model with treatment group (three levels; Placebo, 0.2 mg/kg/day, 0.8 mg/kg/day) and weight group (<37.5 kg, ≥37.5 kg) as factors, log baseline DSF_B as a covariate and log ($CDSF_{T+M}$ +1) as response. Treatment group mean differences from placebo will be estimated via least squares means from the analysis model along with 95% confidence intervals. Since the least square means and confidence intervals will be on the log scale, these least square means and confidence intervals will be exponentiated back to the original scale.

The null hypothesis

$$H_0: m_{Z0.8} - m_P = 0,$$

will be tested against the alternative

$$H_A: m_{Z0.8} - m_P \neq 0,$$

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

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

```
proc glm data=temp;
        class wtgrp trtp;
        model cdsf = bdsf wtgrp trtp  / SS3;
        lsmeans  trtp / pdiff stderr;
```

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

bdsf = log(DSF_B +1),
cdsf = log(DSF_{T+M} +1)
wtgrp = weight group.

Additional statements may be used to obtain estimates and associated 95% confidence intervals. Endpoints of the confidence interval (CIs) will be translated to the original scale using the ranks.

M Period only:

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

Similar non-parametric and parametric ANCOVA models will be used.

Treatment by baseline seizure category interaction:

Treatment by baseline seizure category interaction: The non-parametric and parametric analysis for the T+M and M period described above will be repeated with baseline seizure frequency as a categorical variable, rather than a covariate, and will include baseline seizure frequency by treatment interaction. Baseline seizure frequency per 28 days will be categorized using tertiles.

8.2.3. Sensitivity Analyses of Part 1 Primary Efficacy Endpoint

Wilcoxon Rank-sum Test

The ZX008 0.8 mg/kg/day group will be compared to the placebo group on the percent change from baseline in seizures resulting in drops using a Wilcoxon rank-sum test. The median difference between the groups, and its 95% confidence interval, will be estimated using the Hodges-Lehmann estimator.

Impact of Antiepileptic Drugs (AED)

Subjects in the study are required to be on stable background therapy. Using the MITT population, an additional nonparametric ANCOVA analysis will be performed to assess the impact on the primary analysis of changes in dose or type of concomitant AED, which are protocol violations that may occur during the course of the study.

For this analysis, each subject will be classified according to the number of concomitant AEDs used during the T+M period. Fisher's exact tests will be used to compare the

active dose groups with the placebo group on the percentage of subjects within each group who have a change in concomitant AEDs.

Per protocol Analysis

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

No Imputation for Seizure Clusters

The primary efficacy ANCOVA will be repeated on the mITT population with no imputation for seizure clusters; i.e., seizure clusters will not be calculated in the frequency of seizures that result in drops.

Exclusion of Outliers

The distribution of the primary endpoint is inherently asymmetric since no subject can have more than a 100% decrease in seizures, but there is no reason a subject couldn't have a 200% or even 1000% increase. In fact, there is no theoretical upper bound to the possible magnitude of an increase in a percent change statistic. To assess the sensitivity of the primary analysis to extreme outliers in percent change in drop seizure frequency, the primary analysis will be repeated excluding any PCDSF value that satisfies Tukey's criterion for a "far out" outlier (Tukey, 1977). Specifically, any PCDSF value that satisfies

$$[\hat{q}_{.25} - 3(\hat{q}_{.75} - \hat{q}_{.25}), \quad \hat{q}_{.75} + 3(\hat{q}_{.75} - \hat{q}_{.25})]$$

will be excluded where $\hat{q}_{.25}$ and $\hat{q}_{.75}$ are the sample lower and upper quartiles of the all PCDSF data combined.

Imputation for Dropouts

Two different methods for imputation of missing values due to subject drop out will be incorporated into the analysis of the primary efficacy endpoint. When referring to frequency in the paragraphs below, it refers to the number of seizure events per 28 days.

S1: Worst value substituted: In this analysis, for a subject who drops out of treatment, if the drop seizure frequency during T+M is lower than the baseline value, the baseline value will be substituted for the subject from the point of withdrawal to the end of the planned duration of T+M. However, if the seizure frequency during T+M is higher than the baseline value, there will be no substitution. The DSF for the planned duration of T+M will then be computed as a weighted mean of the value before dropout, and the imputed value after dropout. The weights will be the proportion of planned duration of T+M before and after dropout. The statistical analysis (nonparametric ANCOVA) described at the start of section 8.2.2 will then be performed on the resulting dataset. Treatment comparisons will be based on the least squares means and standard errors obtained from the ANCOVA.

S2: Differential imputation method: In this analysis, subjects who dropout due to an adverse event, lack of compliance, loss to follow-up or subject choice will have their

convulsive seizure frequency for the remainder of the time during the planned T+M period replaced with the worse of the observed value or the baseline value as described for S1. However, for other withdrawal reasons (e.g., "lack of efficacy") their observed DSF during T+M will be imputed for the remainder of the time between dropout and end of planned T+M. The DSF for the planned duration of T+M will then be computed as a weighted mean of the value before dropout and the imputed value after dropout. The weights will be the proportion of time before and after dropout. The statistical analysis (nonparametric ANCOVA) described at the start of section 8.2.2 will then be performed on the resulting dataset. Treatment comparisons will be based on the least squares means and standard errors obtained from the ANCOVA.

Criteria for Establishing Efficacy

While several supportive and/or supplementary analyses are specified above, the main criterion for demonstrating efficacy will be the primary non-parametric analysis for the mITT population from Cohort A.

8.2.4. Key Secondary Analysis of the Primary Efficacy Endpoint

The first key secondary endpoint compares treatment groups on the percentage of subjects with at least a 50% reduction from baseline in seizures resulting in drops. That is, the proportion of subjects in the ZX008 0.8 mg/kg/day group who have a decrease in frequency of seizures resulting in drops of at least 50 percentage points will be compared to the analogous proportion in the placebo group. This the 1st key secondary efficacy endpoint.

The comparison of the percentage of subjects with at least a 50 percent drop from baseline between treatment groups will be made using a logistic regression model that incorporates the factors treatment and weight strata and the baseline seizure frequency. Separate models will be fit for ZX008 0.2 mg/kg/day vs. placebo and ZX008 0.8 mg/kg/day vs. placebo. Achievement of the 50 percentage point reduction or greater, yes or no) will be modeled as a function of treatment group (2 levels; ZX008 0.8 mg/kg/day (or ZX008 0.2 mg/kg/day) and placebo) and baseline weight strata group (<37.5 kg, ≥ 37.5 kg). If the model with treatment and weight strata is not convergent (e.g. due to a 0 count in a treatment by weight strata combination, the model will be refit using treatment only and the baseline seizure frequency. If the model still does not converge, no odds ratio and p-value from the logistic regression will be reported.

The model estimated odds ratio (including a 95% confidence interval) and p-value for comparison of ZX008 0.8 mg/kg/day to placebo and ZX008 0.2 mg/kg/day to placebo will be provided. A supplementary Fisher's exact test comparing treatment groups will be provided.

Similarly, the number and percentage of subjects who have a worsening, ≥0% reduction, ≥25% reduction, ≥50% reduction, ≥75% reduction, 100% reduction, and near seizure-freedom will be tabulated for each treatment. Near seizure-freedom will be defined as having 0 or 1 seizures leading to a drop in the T+M period. These are additional secondary endpoints.

8.3. KEY SECONDARY EFFICACY ENDPOINTS AND ANALYSES

8.3.1. 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: at the end of the Titration period Visit 6 (Day 15), during the Maintenance period at Visit 8 (Day 43) and Visit 10 (Day 71), and at Visit 12 (End of Study / Early Termination).

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

The mean (SD) CGI-I score, and the number and percentage of subjects who showed improvement (i.e., had a score of 3 or lower), and the number and percentage who did not improve (i.e., had a score of 4 or higher) will be presented for each for each treatment group at each assessment time point. Each assessment time point will include a comparison between each active treatment and the placebo group using the Cochran-Mantel-Haenszel test (CMH) stratified by weight strata, and a frequency distribution of the number and percentage of subjects in each category in the scale. A graphic showing the percentage of respondents in each category will be presented.

The number and percentage of subjects who showed clinically meaningful improvement (i.e., had a score of 2 or lower), and the number and percentage who did not have clinically meaningful improvement (i.e., had a score of 3 or higher) will be presented for each treatment group at each assessment time point as an exploratory analysis.

Individual subject CGI data will be listed.

8.4. ADDITIONAL EFFICACY ENDPOINTS AND ANALYSES

8.4.1. Countable Motor Seizures Definition and Analysis

The change in the frequency of countable motor seizures per 28 days between the Baseline and T+M periods will be calculated using the same methodology described for the primary endpoint. Countable motor seizures include:

- generalized tonic-clonic seizures [GTC]
- secondarily generalized tonic-clonic [SGTC]
- tonic seizures [TS]
- atonic seizures [AS]
- tonic/atonic seizures [TA]
- clonic seizures [CS]
- hemiclonic seizures [HS]
- focal seizures [FS] with clear observable motor signs

A change in the frequency of countable motor seizures per 28 days between the Baseline and M period will also be calculated.

The same non-parametric and parametric ANCOVA models described for the primary endpoint will be used for the analyses of countable motor seizures (change in the frequency between Baseline and T+M periods). The mITT population will be used for this analysis. The difference between 0.8 mg/kg/day and placebo in the change between Baseline and T+M is a secondary endpoint. The analyses will be repeated for the change in frequency between the Baseline and M periods. The analysis of the change between Baseline and the M period is one of the additional secondary endpoints.

The number and percentage of subjects who had a worsening, 0% reduction, ≥25% reduction, ≥50% reduction, ≥75% reduction, and 100% reduction in the frequency of countable motor seizures between Baseline and T+M and between Baseline and M will be summarized by treatment group and overall. These analyses are part of the additional secondary endpoints.

8.4.2. Additional Seizure Counts

The other efficacy endpoints of change in the frequency per 28 days between Baseline and T+M peropd and between Baseline and M period of:

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

Each of these endpoints will be calculated using the same method as the primary endpoint. The same non-parametric ANCOVA, parametric ANCOVA, and logistic regressions used for the primary efficacy endpoint will be used. The mITT population and PP populations will be used for these analyses.

Refer to Appendix 1 for the seizure types that are included in each of these endpoints.

8.4.3. 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 day without countable motor seizures will be defined as a day for which diary data are available and with no countable motor seizures. The total number of countable seizure-free days and drop seizure-free days will be summed for the entire T+M period and similarly for the baseline period.

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

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

Statistical comparison of treatment groups and placebo on the number of seizure free days per 28 days and drop seizure-free days per 28 days during T+M using the baseline as covariate will be done with a similar non-parametric ANCOVA model as described for the primary analysis.

8.4.4. 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, the duration of the longest interval between seizures resulting in drops (i.e., ESC confirmed) will be calculated over the entire T+M 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 convulsive seizures will be derived.

If a subject has a missing diary day within an otherwise seizure-free interval, that day is counted towards the duration of the seizure free interval. However, if a subject has two consecutive days of missing diary data, the current seizure-free interval will end on the first date of missing diary data, and a new one begun on the next date that diary data are available and no seizure occurs. [In that case, for purpose of calculation of this variable, all intervening days, after the 2nd day, with missing diary data, will be assumed to have a seizure with drops 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 maintenance period, where LDT ≥ Date5, then the time interval between convulsive seizures will be calculated as follows:

I1=Date2 - Date1

I2=Date3 - Date2

I3=Date4 – Date3,

I4=Date5 – Date4.

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

I0=Date1 – Date0,

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

I5 = LDT – Date5.

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

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

The longest interval=last available diary date – Date0

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

The Wilcoxon rank sum test will be used to test for differences between each treatment arm and placebo, and the p-value from this test will be presented. A boxplot summarizing the duration of the longest interval between seizures will be provided.

8.4.5. 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-I score data recorded by Principal Investigator as above.

8.4.6. Incidence of Status Epilepticus

The incidence of status epilepticus (SE) will be evaluated based on: 1.) those entered as serious adverse events, and 2.) Seizures lasting longer than 10 minutes from the seizure diary. A single seizure meeting more than one of these criteria will be counted once.

The number and percentage of subjects with SE during the baseline and T+M period recorded as an AE will be presented by treatment group. Statistical comparisons of the difference in incidence will be tested using a Fisher's Exact Test.

From the diary data, change from baseline in the number of seizures with duration > 10 minutes per 28 days for the baseline and T+M period will be reported. A nonparametric ANCOVA will be completed to compare active groups vs. placebo. As well, the number of unique days where status epilepticus was reported (normalized per 28 days) will be summarized and analyzed using the nonparametric ANCOVA.

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

A second calculation will present the number of incidences of SE, according to the above definition, by treatment group normalized to per 28 days. In this analysis, a single subject may have more than one episode of SE, but an episode of SE recorded as both an AE and as a seizure longer than 10 minutes will be counted as a single episode. Statistical comparisons of the differences between treatment and placebo groups will be based on a Fisher's Exact Test. A difference in percentages between baseline and the T+M period will be calculated and summarized within each treatment group.

8.4.7. Rescue Medication Usage

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

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

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

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

8.4.8. Incidence of Medical Services to Treat Seizures

Data on hospitalization and healthcare resource use to treat seizures 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 will be summarized. The number and percentage of subjects who utilized medical center care to treat a seizure will be presented by treatment group for the T+M period. The mean, median, min and max describe the number of events or procedures per subject for those subjects who had at least one event or procedure.

Statistical comparisons of the incidence of use of medical services between active and placebo groups will be provided using Fisher's exact test.

8.4.9. Vineland Adaptive Behavior Scale (VABS)

The VABS is a parent/caregiver completed assessment that looks at the personal and social skills of individuals from birth through adulthood (Sparrow, S. S. & Cicchetti, D. V. (1989)). Because adaptive behavior refers to an individual's typical performance of the day-to-day activities required for personal and social sufficiency, these scales assess what a person actually does, rather than what he or she is able to do. The VABS assesses adaptive behavior in 4 domains:

- Communication
- Daily living skills
- Socialization
- Motor skills

In Part 1, the VABS is collected at Visit 3 (Randomization), Visit 8 (Day 43), and Visit 12 (End of Study/Early Termination).

At each assessment, the standardized domain scores will be determined.

For each domain, the change from baseline for each subject will be calculated by subtracting the domain score measured at Baseline from the analogous score measured at Visit 8 (Day 43) and Visit 12 (End of Study /Early Termination). Observed values and change from baseline will be summarized by descriptive statistics. The difference between treatment groups will be assessed using pairwise Wilcoxon rank-sum tests on the change from baseline.

The individual item outcomes and standardized domain scores will be presented in the subject data listing.

8.4.10. Quality of Life in Childhood Epilepsy (QOLCE) Scale

The parent/caregiver will complete 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.

The QOLCE is collected at Visit 3 (Randomization) and at Visit 12 (End of Study/Early Termination).

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.

Summary descriptive statistics including the n, mean, standard deviation, median, minimum, and maximum will be generated for the index score at each scheduled collection time point.

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

Table 6: 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.

For each treatment group and at each schedule visit, the descriptive statistics will be presented for each QOLCE subscale and for the overall quality of life score.

In addition, the change from baseline in the overall QOLCE will be calculated for each subject by subtracting the Part 1 baseline score from the score measured at each scheduled post-baseline visit. The change from baseline for each treatment group will be summarized by summary statistics. Treatment groups will be compared using pairwise Wilcoxon Rank-sum tests.

Individual subject data for the domains will be listed.

8.4.11. Zarit Caregiver Burden Inventory

[redacted]

[redacted]

8.4.12. Patient/Caregiver Assessment using HADS Scale

[redacted]

[redacted]

9. SAFETY

All Part 1 safety analyses will be performed for the Safety population (SAF), as defined in Section 6.2 . Results will be reported by treatment group for the 16-week treatment period, unless noted otherwise.

9.1. EXTENT OF EXPOSURE

Part 1 treatment exposure data will be summarized for the SAF population.

Duration of total exposure during Part 1 (i.e., time on treatment (in days)) will be calculated per subject as the number of days with IMP intake during the trial and will be summarized using n, mean, standard error, median, minimum, Q_1, Q_3 and maximum.

This will be calculated for non-placebo subjects as:

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

Time on treatment will be summarized by the Part 1 treatment group.

9.2. TREATMENT COMPLIANCE (DIARY)

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

A compliance will also be determined based on the actual quantity taken, determined using the weight of the dispensed drug kit 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 1, compliance will be summarized for the SAF and mITT populations over the course of T+M period and M period only per recorded visit dates, reported by treatment group.

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, whether or not considered related to the medicinal (investigational) product. For Part 1, the period of observation for adverse events extends from the time the subject gives informed consent until the end of the titration/transition period (Visit 13 or 15).

A treatment-emergent adverse event (TEAE) in Part 1 is defined as any AE that based on start date information occurs after the first intake of study treatment in Part 1, but not on or after the first dose of study treatment in Part 2. For subjects who participate in Part 2, the Part 1 TEAE will include events with onset up to the day prior to the date of first dosing in Part 2. A Part 1 TEAE will be further classified into the Titration Period, Maintenance Period, and Transition/Taper Period. The Titration Period will include all events with onset from the date of the first dose in Part 1 to date of the Visit 6. The Maintenance period will include all events with onset from the day after Visit 6 through the date of Visit 12. The Transition/Taper period will include all events with onset starting with the day after Visit 12 through Visit 15.

For Part 1, tables will present TEAE data by assigned treatment group received in Part 1. AEs occurring after enrollment and prior to the first administration of study treatment in Part 1 are defined as non-treatment emergent AEs (non-TEAEs).

AEs are categorized as related or unrelated. If the AE is thought to be definitely, probably or possibly related to study drug then it is to be categorized as related. Possibly or definitely unrelated is categorized as unrelated. Any 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 follows:

Severity Definition of Adverse Events:

Mild - A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate - A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe - A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

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

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

9.3.1. Overview of Adverse Events

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

- TEAE
- Related TEAE
- Serious TEAE

- Related serious TEAE
- Severe TEAEs
- Severe related TEAE
- Adverse events of special interest
- TEAEs leading to premature discontinuation of study treatment
- TEAEs leading to premature discontinuation from the study
- Death

This overall summary table will be presented for the full Part 1 period, Titration Period, Maintenance Period, Titration + Maintenance Period, and Taper/Transition Period.

For the full Part 1 period, Titration Period, and Titration + Maintenance Period, the denominator for the calculation of percentage will be the number of subjects in the SAF for the treatment group. For the Maintenance Period, the denominator for the calculation of the percentage will be the number of subjects for the treatment group with Part 1 last dose strictly greater than the date of Visit 6. For the Taper/Transition Period, the denominator for the calculation of the percentage will be the number of subjects for the treatment group with last dose strictly greater than the date of Visit 12.

9.3.2. Treatment Emergent Adverse Events

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

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

These summaries will present the TEAEs presented for the full Part 1 period, Titration Period, Maintenance Period, Titration + Maintenance Period, and Taper/Transition Period.

Summaries of TEAEs and Study Drug Related TEAEs will be summarized for the following subgroups:

- Age: 2– <6 years, 6–<12 years, 12 - <18, ≥ 18 – 35 years.
- Sex

- Concomitant usage of most commonly used concomitant Anti-epileptic medications (e.g. Valproate or other medications of interest; to be determined)
- # of con AEDs

One additional summary table will summarize the number and percent of subjects in each treatment group who experience an AE that occurs in at least 5% of subjects in any treatment group. For AEs occurring in at least 5% of subjects, the mean and median time to onset and the median duration of the onset will be presented. The summary will be presented by preferred term in decreasing order of incidence.

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

The following listings will be produced for all enrolled subjects:

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

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

Standardized MedDRA Queries (SMQs) will be employed as applicable to identify each AESI category or manually assigned through review. For Part 1 AEs, this will be completed and documented prior to study unblinding.

For Part 1, adverse events of special interest will be summarized by treatment group and by system organ class and preferred term.

All AESIs will be listed separately.

9.4. PHYSICAL EXAMINATION

A complete physical examination will be performed at Screening Visit (Visit 1), Visit 3 (Randomization) prior to first dose of study medication, and at the Visit 12 (End of

Study/Early Termination). An abbreviated physical exam is performed at Visit 6 (Day 15), Visit 8 (Day 43), and Visit 10 (Day 71). A complete or abbreviated physical exam may be performed at the Cardiac follow-up visit for subjects who do not enter the open-label extension study if clinically warranted. Clinically significant findings at screening will be reported on the medical history page. New clinically significant findings starting with after the first dose in Part 1 will be reported as adverse events.

A summary of subjects with clinically significant physical examination findings at each visit will be provided for the T+M period.

All physical examination results will be presented in a subject data listing.

9.5. NEUROLOGIC EXAMINATION

In Part 1, a complete neurological examination will be performed at Visit 1 (Screening) and Visit 12 (End of Study / Early Termination). An abbreviated neurological examination will be performed at Visit 3 (Randomization) and at Visit 6 (Day 15), Visit 8 (Day 43), and Visit 10 (Day 71). Clinically significant findings at screening will be reported on the medical history page. New clinically significant findings starting with after the first dose in Part 1 will be reported as adverse events.

A summary of subjects with clinically significant neurologic examination findings at each visit will be provided for the T+M period.

All neurological examination results will be presented in a subject data listing.

9.6. VITAL SIGNS, WEIGHT, AND BMI

Vital signs data will be documented for subjects during study at screening visit (Visit 1), Visit 3 (Randomization) prior to first dose of study medication, at the end of the titration period at Visit 6 (Day 15), during the maintenance period at Visit 8 (Day 43) and Visit 10 (Day 71), and at Visit 12 (End of Study / Early Termination). The measurements will include blood pressure, heart rate, temperature, respiratory rate, weight, and BMI.

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

For weight and BMI, the occurrence of at least a ≥ 7% gain/reduction or ≥ 10% gain/reduction from baseline will be summarized by visit and at any time during the T+M treatment period. For subjects with an occurrence of a ≥ 7% reduction in weight or BMI, the number who achieved a recovery to their baseline weight, and the duration of time to recovery, will be summarized, and whether that recovery was achieved as a result of a reduction or withdrawal of the subject's study medication. Recovery will be defined as achieving a weight after the >= 7% reduction, that is at least 99% of the baseline weight and having a weight at Visit 12 that is at least 99% of the baseline weight. The number of days until weight recovery will be determined using the date of the first date where the weight loss was observed and the first date where the subject's weight had recovered to, and maintained for the duration of the study period, at least 99% of the baseline weight.

For subjects with at least a 7% reduction in body weight, a spaghetti plot of showing the subject's weight values by study day will be presented by actual treatment group.

Vital signs, Weight and BMI data will be presented in a data listing.

For each subject with a clinically meaningful abnormality in vital signs, (to be supplied by Zogenix International), a table will be produced organized by parameter that lists each subject, age, sex, day of most abnormal value, the most abnormal value, and the reference range, and first date of a normal value (occurring after the abnormality).

A listing of subjects with at least a 7% reduction in weight/BMI and clinically meaningful abnormal values will be created.

9.7. ELECTROCARDIOGRAM

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

9.8. DOPPLER ECHOCARDIOGRAPHY

Results of ECHOs will be presented in a separate report from ERT (formerly Biomedical Systems).

9.9. TANNER STAGING

In Part 1, Tanner Staging will be assessed for subjects > 7 to 18 years old during the study at Visit 3 (Randomization) and Visit 12 (End of study / Early Termination).

Conceptually, pubertal maturation can be described in terms of sequence, timing, and tempo. Puberty consists of a series of predictable events, and the sequence of changes in secondary sexual characteristics has been categorized by several groups. The onset and progress of pubertal changes will be recorded on a 5-point scale for boys and girls separately. Boys are rated for genital development and pubic hair growth through stage I to stage V. Girls are rated for breast development and pubic hair growth through stage I to stage V.

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

9.10. 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 4.

The following continuous laboratory parameters will be analyzed:

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

Observed continuous laboratory data will be descriptively summarized by type of laboratory test/parameter change from baseline.

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

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

- below lower limit of normal and clinically significant
- below lower limit of normal,
- within normal limits,
- above upper limit of normal,
- above upper limit of normal and clinically significant.

Listings of the most extreme values for a subject recorded in Part 1 and Part 2 will be created for each parameter. These will show the lowest recorded value and the highest recorded value noted for the subject. A listing of subjects with markedly abnormal laboratory results will be provided, and additional explorations of the data may be conducted as warranted.

Additionally, summaries of abnormal lab results by parameter will be provided to investigate changes in platelet count and prolactin in detail. The summaries include:

- Subjects with decrease (≥25% from baseline) in Platelets count with normal platelet count at baseline
- Subjects with decrease (≥25% from baseline) in Platelets count relative to baseline (whether normal or abnormal) platelet count
- Subjects with decrease (≥25% from baseline) in Platelets count with normal platelet count at baseline, by valproate use
- Subjects with decrease (≥25% from baseline) in Platelets count with normal platelet count at baseline, by presence/absence of infection event prior to 7 days of the lab assessment
- Subjects with increase (≥25% from baseline) in prolactin with normal baseline
- Subjects with increase (≥25% from baseline) in prolactin with normal baseline, and had seizure event within 48 hours prior to prolactin

9.11. COLUMBIA-SUICIDE SEVERITY RATING SCALE

During Part 1, the Columbia-Suicide Severity Rating Scale (C-SSRS) data will be collected as per at screening visit (Visit 1), at randomization (Visit 3), at the end of the Titration period at Visit 6 (Day 15), during the Maintenance period at Visit 8 (Day 43) and Visit 10 (Day 71), and at Visit 12 (End of study/Early Termination).

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 outcomes are C-SSRS categories for [redacted] and have binary responses (yes/no):

Category	Outcome Description
1	[redacted]
2	
3	
4	
5	

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

[redacted]

The following outcomes are C-SSRS categories for [redacted] and have binary responses (yes/no):

Category	Outcome Description
6	[redacted]
7	
8	
9	
10	

[redacted] is assessed as a "yes" answer at any time during the T+M period to any one of the five questions (6-10) above. In Part 1, the number and percentage of subjects who had [redacted], as well as the number and percentage having a "yes" response to each category (6-10) at least once during the T+M period. The denominator will be the number of subjects completing the C-SSRS at least once during the T+M period.

[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' anything during the T+M period for Part 1.

[redacted]

For Part 1, the number and percentage of subjects having reported anytime during the T+M period experiencing a [redacted] event (Question 11) will be provided.

9.12. BRIEF RATING INVENTORY OF EXECUTIVE FUNCTION (BRIEF)

[redacted]

10. INTERIM ANALYSES

No formal interim analysis is planned for this study. However, the analysis of the Part 1 Cohort A will occur prior to the completion of Part 1 Cohort B. The unblinding of Part 1 Cohort A will not occur until data cleaning is completed and all decisions regarding protocol deviations warranting exclusion from the per protocol population have been made for the Cohort A subjects. The review of deviations and exclusion from the per protocol population for Cohort B subjects will occur independently. An unblinded team from Zogenix International and Syneos Health will be assigned to complete the unblinding of Part 1 Cohort A. The unblinded team will not participate in any decision-making regarding the Cohort B subjects' Part 1 data. Access to aggregated data (i.e. group-level tables or figures) does not constitute unblinding and for the purpose of data cleaning these subjects will be considered blinded. A separate unblinding plan will be developed to further define this process.

11. CHANGE FROM PLANNED ANALYSES

There have been several changes to the Additional Secondary Objectives specified for Part 1, Cohort A in the protocol, and consequently to the associated Additional Secondary Efficacy Endpoints. These mainly fell into the following categories:

- Addition of new objectives
- Clarification of seizure types involved
- Specification of when seizure types needed ESC confirmation
- Clarification of the treatment period involved.

The following is a list of the Additional Secondary Objectives as specified in the protocol and as specified in the SAP to summarize changes:

Protocol Version 2.1	**Statistical Analysis Plan Version 1.1**
To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the following endpoints:	To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the following endpoints:
	Added: • Change in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) between baseline and the combined T+M whether ESC confirmed as drop or not.
• Change in the frequency of all countable motor seizures between baseline and T+M (countable seizures include: generalized tonic-clonic seizures [GTC], tonic seizures [TS], clonic seizures [CS], atonic seizures	*Modified to:* • Change in the frequency of all countable motor seizures between baseline and T+M (countable seizures include: GTC, SGTC, TS, AS, TA, clonic

[AS], tonic/atonic seizures [TA], clearly recognizable focal seizures [FS], and myoclonic seizures [MS] that result in a drop).	seizures [CS], focal seizures with clear observable motor signs [FS], and hemiclonic seizures [HS]).
• Change in the frequency of all countable seizures (ie, motor and nonmotor) between baseline and T+M	• Change in the frequency of all countable seizures (i.e., motor and non-motor) between baseline and T+M
• Change in frequency of seizures that result in drops between baseline and the Maintenance Period (M)	*Modified to:* • Change in frequency of seizures that result in drops (ESC confirmed) between baseline and the Maintenance Period (M)
	Added: • Change in frequency of seizures that (typically) result in drops between baseline and the Maintenance Period (M)
• Change in the frequency of countable motor seizures that do not result in drops between baseline and M	*Deleted and replaced with:* • Change in the frequency of all countable motor seizures between baseline and M • Change in the frequency of all countable non-motor seizures between baseline and M • Change in the frequency of all countable seizures (i.e., motor and non-motor) between baseline and M
• The proportion of subjects who have a worsening or no change (ie, ≤ 0% reduction), >0%, ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (ie, 0 or 1 seizures) between baseline and T+M, and baseline and M, in all countable motor seizures (GTC, TS, AS, TA, FS, MS with a drop); in countable motor seizures that do not result in drops; in all countable seizures; in all countable seizures that do not result in drops; and in all seizures that result in drops	*Modified to:* • The proportion of subjects who achieve a worsening, >0 - <25%, ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (i.e. 0 or 1 seizures) between baseline and T+M, and baseline and M, in 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 countable seizures and	*Modified to:*

2) days with no seizures that result in drops	• Number of seizure-free days, defined as 1) no seizures that result in drops (ESC confirmed), and 2) days with no countable motor seizures
• Longest interval between seizures that result in drops	*Modified to:* • Longest interval between seizures that result in drops (ESC confirmed)
• To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver	• To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the parent/caregiver.

Below is a list of the Additional Secondary Efficacy Endpoints as specified in the protocol:

Protocol Version 2.1	**Statistical Analysis Plan Version 1.1**
	Added: • Change from baseline during T+M in frequency of all seizures that (typically) result in drops (i.e., GTC, SGTC, TS, AS, TA) whether ESC confirmed as drop or not.
• Change from baseline in the frequency of all countable motor seizures in T+M • Countable seizures include: generalized tonic-clonic seizures [GTC], tonic seizures [TS], clonic seizures [CS], atonic seizures [AS], tonic/atonic seizures [TA], clearly recognizable focal seizures [FS], and myoclonic seizures [MS] that result in a drop	*Modified to:* • Change from baseline during T+M in frequency of all countable motor seizures (GTC, SGTC, TS, AS, TA, CS, FS, and HS).
• Change from baseline in the frequency of countable seizures that result in drops	*Modified to:* • Change from baseline during T+M in the frequency of all countable seizures (i.e., motor and non-motor).
• Change from baseline in the frequency of seizures that result in drops between baseline and the Maintenance Period (M)	• Change from baseline during M in the frequency of seizures that result in drops.

• Change from baseline in the frequency of countable seizures that do not result in drops	*Deleted*
	Added: • Change from baseline during T+M in frequency of all countable non-motor seizures (absence, myoclonic, focal without clear observable motor signs, infantile spasms, and epileptic spasms). • Change from baseline during M in the frequency of seizures that typically result in drops. • Change from baseline during M in the frequency of all countable motor seizures. • Change from baseline during M in the frequency of all countable non-motor seizures. • Change from baseline during M in the frequency of all countable seizures (i.e., motor and non-motor).
• Proportion of subjects who achieve a worsening from baseline (ie, ≤ 0% reduction), or >0% , ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (ie, 0 or 1 seizures) between baseline and T+M, and baseline and M, in all countable motor seizures; in countable motor seizures that do not result in drops; in all countable seizures; in all countable seizures that do not result in drops; and in all seizures that result in drops	*Modified to:* • Proportion of subjects who achieve a worsening from baseline (i.e. ≤ 0% reduction), or >0%, ≥25%, ≥50%, ≥75%, or 100% reduction between baseline and T+M, and baseline and M, in 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 in the baseline, M, and T+M period, 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 in the baseline, M and T+M period, defined as 1) days with no seizures that results in drops (ESC confirmed), and 2) days with no countable motor seizures
• The longest interval (days) between seizures that result in drops comparing	*Modified to:*

the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo	• The longest interval (days) between seizures that result in drops (ESC confirmed) comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo
• Clinical Global Impression – Improvement as assessed by the parent/caregiver	• Clinical Global Impression – Improvement as assessed by the parent/caregiver

12. 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.

12.1. 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.

12.2. TABLE, LISTING, AND FIGURE FORMAT

12.2.1. 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.

12.2.2. 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.

12.2.3. 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

12.2.4. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.
- For numeric variables, include "unit" in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

12.2.5. Body of the Data Display

12.2.5.1. 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.

12.2.5.2. Table Conventions

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category 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 with the highest occurrence in decreasing order, 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 in decreasing order. 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 treatment groups as above, 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

12.2.5.3. 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.

12.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Subject specific footnotes 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').

13. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. Syneos Health SOP 03.010 and 03.013 provide an overview of the development of such SAS programs.

Syneos Health SOP 03.009 describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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The data analyses from Cohort B subjects in Japan will not be performed during the initial, principal analysis of the trial but will be conducted later. In general, the same analyses that apply to Cohort A subjects in North America, Europe and Australia will be applied to Cohort B subjects in Japan except for those where the smaller sample size in Cohort B makes the analysis untenable. In particular, subset analyses will not be applied to Cohort B data.

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Output	16.2.9.2.1.3.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population
Output	16.2.9.2.1.4.1.1	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – mITT Population
Output	16.2.9.2.1.4.1.2	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort B – Japan) – mITT Population
Output	16.2.9.2.1.4.2.1	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – PP Population
Output	16.2.9.2.1.4.2.2	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort B – Japan) – PP Population
Output	16.2.9.2.1.6.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Age Subgroup: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population
Output	16.2.9.2.1.6.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Sex: Nonparametric Analysis – (Cohort A – North America, Europe, Australia) mITT Population
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Output	16.2.9.2.1.6.6	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Baseline Frequency of Seizures that Result in Drops: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population
Output	16.2.9.2.1.7.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 1 (Worst Value Substituted for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population
Output	16.2.9.2.1.7.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 1 (Worst Value Substituted for Dropouts) (Cohort B – Japan) – mITT Population
Output	16.2.9.2.1.7.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 2 (Differential Imputation Method for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population
Output	16.2.9.2.1.7.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 2 (Differential Imputation Method for Dropouts) (Cohort B – Japan) – mITT Population
Output	16.2.9.2.1.9.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort A – North America, Europe, Australia) – mITT Population
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Output	16.2.9.2.3.2.1.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population
Output	16.2.9.2.3.2.2.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population
Output	16.2.9.2.3.2.2.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population
Output	16.2.9.2.3.3.1.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia)– mITT Population
Output	16.2.9.2.3.3.1.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population
Output	16.2.9.2.3.3.2.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population
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Output	16.1.9.2.4.1.2.1.2	Frequency of Typical Drop Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population
Output	16.1.9.2.4.1.2.2.1	Frequency of Typical Drop Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population
Output	16.1.9.2.4.1.2.2.2	Frequency of Typical Drop Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population
Output	16.1.9.2.4.1.3.1.1	Frequency of Typical Drop Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population
Output	16.1.9.2.4.1.3.1.2	Frequency of Typical Drop Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population
Output	16.1.9.2.4.1.3.2.1	Frequency of Typical Drop Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population
Output	16.1.9.2.4.1.3.2.2	Frequency of Typical Drop Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population
Output	16.1.9.2.4.1.4.1.1	Percent Improvement in Frequency of Typical Drop Seizures per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population

Output	16.1.9.2.4.1.4.1.2	Percent Improvement in Frequency of Typical Drop Seizures per 28 days during Part 1: Logistic Regression (Cohort B – Japan)– mITT Population
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Output	16.1.9.2.4.2.2.1.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population
Output	16.1.9.2.4.2.2.1.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population
Output	16.1.9.2.4.2.2.2.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population
Output	16.1.9.2.4.2.2.2.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population
Output	16.1.9.2.4.2.3.1.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population
Output	16.1.9.2.4.2.3.1.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population
Output	16.1.9.2.4.2.3.2.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population
Output	16.1.9.2.4.2.3.2.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population
Output	16.1.9.2.4.2.4.1.1	Percent Improvement in Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population
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Output	16.1.9.2.4.3.2.2.1	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population
Output	16.1.9.2.4.3.2.2.2	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population
Output	16.1.9.2.4.3.3.1.1	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population
Output	16.1.9.2.4.3.3.1.2	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population
Output	16.1.9.2.4.3.3.2.1	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population
Output	16.1.9.2.4.3.3.2.2	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population
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16. APPENDICES

16.1. APPENDIX 1 – SEIZURE TYPES

1. All Seizures	2. Countable Motor Seizures	3. Countable Non-Motor Seizures	4. Drop Seizures (ESC confirmed or Typical)
Generalized Tonic-Clonic	Generalized Tonic-Clonic		Generalized Tonic-Clonic
Secondarily Generalized Tonic-Clonic	Secondarily Generalized Tonic-Clonic		Secondarily Generalized Tonic-Clonic
Tonic	Tonic		Tonic
Atonic	Atonic		Atonic
Tonic/Atonic	Tonic/Atonic		Tonic/Atonic
Clonic	Clonic		
Hemiclonic	Hemiclonic		
Focal with clear observable signs	Focal with clear observable signs		
Focal without clear observable signs		Focal without clear observable signs	
Myoclonic		Myoclonic	
Absence/atypical absence		Absence/atypical absence	
Infantile Spasms		Infantile Spasms	
Epileptic Spasms		Epileptic Spasms	
Other		Other	

16.2. 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 (ie, 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 version 1.1 of the 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.

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.

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 Version 1.1
Date of SAP:	January 23, 2020
SAP Prepared by:	ERT (Formerly Biomedical Systems)
Sponsor:	Zogenix International Limited A subsidiary of Zogenix, Inc. 5858 Horton Street, Suite 455 Emeryville, CA 94608 USA

SAP Approval

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 23-Jan-2020 | 5:11:12 PM PST
[redacted]
Date

Statistician

DocuSigned by:
[redacted]
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Senior Principal Imaging Statistician

Zogenix International Limited

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Signing Time: 23-Jan-2020 | 4:53:44 PM PST
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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
ΔΔHR	Change from baseline and placebo in Heart Rate
ΔΔPR	Change from baseline and placebo in the PR-interval
ΔΔQRS	Change from baseline and placebo in the QRS duration
ΔΔQTcF	Change from baseline and placebo in the QTcF interval
ACI	Abnormal Clinically Insignificant
ANOVA	Analysis of Variance
APCS	Abnormal Potentially Clinically Significant
bpm	Beats per minute
CAMI	Computer Assisted Measurement of Intervals
C_{max}	Maximum Plasma Concentration
CI	Confidence Interval
DSF	Drop Seizure Frequency
ECHO	Echocardiograms
ECG	Electrocardiogram
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)
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

Study ZX008-1601 is investigating ZX008, an oral solution of fenfluramine hydrochloride, for the treatment of seizures associated with Lennox-Gastautsyndrome.Lennox-Gastaut syndrome is a rare epileptic encephalopathy. The onset of Lennox-Gastaut syndrome occurs most commonly before age 11, with a peak between 3 and 5 years of age (Arzimanoglou 2009; Hancock 2013). Patients with Lennox-Gastaut syndrome 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 Lennox-Gastaut syndrome patients include atypical absences, nonconvulsive seizures, focal seizures, and myoclonic seizures. Nearly all patients have treatment-resistant, lifelong epilepsy. Patients with Lennox-Gastaut syndrome 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 Lennox-Gastaut syndrome 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: ie, 2 to 4 times higher than the proposed maximum daily dose for Dravet syndrome and Lennox-Gastaut syndrome. 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.

In addition to Lennox-Gastaut syndrome, Zogenixis investigating ZX008 for the

treatment of seiures associated with Dravet syndrome. Zogenix has reported safety and efficacy data from 2 adequate and well controlled studies in patients with Dravet syndrome, Study 1 and Study 1504 Cohort 2, and 1 interim analysis from the open-label extension study (Study 1503). Study 1 compared 2 doses of ZX008, 0.2 mg/kg/day and 0.8 mg/kg/day (up to a maximum of 30 mg/day), to placebo in subjects receiving standard of care anti-epileptic treatments excluding stiripentol (STP). Study 1504 Cohort 2 compared a dose of ZX008 0.5 mg/kg/day (up to a maximum of 20 mg/day) to placebo in subjects receiving standard of care anti-epileptic treatments where administration of STP (in combination with clobazam [CLB] and/or valproate [VPA]; ie, the STP regimen) was mandatory.

Both studies met the primary efficacy endpoint and all key secondary efficacy endpoints. In both 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 both Phase 3 studies demonstrated that ZX008 was [redacted] and well tolerated at doses up to 30 mg/day administered in the ZX008 clinical program.

A prospectively-defined cardiovascular monitoring program that employed color Doppler echocardiography (ECHO) was implemented in the ZX008 clinical program (all Dravet syndrome and Lennox-Gastaut syndrome [LGS] trials) to monitor for valvular heart disease (VHD) or pulmonary artery hypertension (PAH); this ECHO program was designed with input from FDA and from cardiology experts.

No VHD, as measured by valve function and observations of valve structure, or PAH, as measured by pulmonary pressure, has developed in any subject in the reported Dravet syndrome trials, nor in fact has any VHD or PAH developed in any subject in the program as of July 2019. Normal nonpathologic trace and mild mitral regurgitation and trace aortic regurgitation were observed in very low rates consistent what has been reported in literature with no subjects progressing to VHD; most of these findings were transient and fluctuated between absent and trace regurgitation during the study. The point prevalence of trace mitral and aortic regurgitation were equal to or lower than the incidence rates reported in normal healthy developing children (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 1 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 are:

- Study Protocol ZX008-1601 (29July 2019, Amendment 2.1).
- Syneos Health-ZogenixZX008-1601Statistical Analysis Plan (Final Version 1.0, 5August 2019).
- ZX008 Investigational Brochure (Version 7.0, July 2019).

The description of methodology of analysis for Part 2 of the study will be provided

in a separate SAP as necessary.

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 Lennox-GastautSyndrome(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.Part 2 is an open-label extension to assess long-term safety of ZX008.

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.

Data from Part 1, Cohort A for cardiovascular endpoints will be analyzed.All other study results for these subjects (demographics, efficacy, safety, PK) will be presented in the Clinical Study Report for ZX008-Study 1601 Part 1.

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.

Echocardiograms will be reviewed by two, board-certified cardiologists. In the case of a discrepancy between the readers, the echocardiogram was sent to adjudicatorsfor 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 ZX008-1601 Part 1is to demonstrate that ZX008 0.8 mg/kg/day is superior to placebo as adjunctive therapy in the treatment of uncontrolled seizuresin children and adults with Lennox-Gastaut syndrome (LGS) based on the change in frequency of seizures that result in drops (drop seizure frequency,DSF) between baseline and the combined Titration and Maintenance Periods (T+M).

2.2.1 Cardiovascular Safety Objectives

The primary cardiovascular safety objective of this analysis is to evaluate the effect of ZX008 on the heart as demonstrated by ECHO.

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

2.3 Endpoints

2.3.1 Echocardiograms

2.3.1.1 Main Focus for Echocardiograms

The main focus for the echocardiographic analysis is the regurgitation score for the mitral and aortic valves at each time-point with the main focus being the development of clinically meaningful (pathologic) changes in valve regurgitation (definitions and thresholds defined below).

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

2.3.1.2 Other Echocardiographic Analyses

Other, secondary endpoints include:

- Number of subjects within each tricuspid or pulmonic regurgitation score by visit
- Number of subjects with normal ortrace tricuspid or pulmonic regurgitation at baseline and ≥ mild tricuspid or pulmonic regurgitation at end of study
- Pulmonary Artery Systolic Pressure (PASP)
    - Mean change from baseline at end of study
    - Mean maximum change from baseline at anytime during therapy
    - Number of subjects with change from baseline at anytime during therapy shows:
        - >10 mmHg
        - >15 mmHg
        - >20 mmHg
    - Number of subjects at anytime during therapy shows
        - 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 msec and at EOS/ET RVOT <100 msec
- Number of patients with any RVOT measurement < 100 msec post-baseline

Summary of the number of ECHOs per subject will also 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.

Subject ID	Visit 1	Visit 8	Visit 12 EOS/ET	Visit 14 Follow-up
1001-001				
1001-002				
1001-003				
1001-004				
1001-005				

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 Focus of ECG Analysis

The primary endpoint will be the mean change between measurements of QT interval corrected using Fridericia'sformula(QTcF) for ZX008 (0.2 mg/kg and 0.8 mg/kg) and placebo after baseline adjustment, (ΔΔQTcF)

2.3.2.2 Other ECG Analyses

The secondary endpoints:

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

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

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

- For all ages QTcF changes from baseline (ΔQTcF, number andpercentage of subjects, by dose)
  - ≤ 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
		> 90ms 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	≤110ms
		>110 ms to ≤ 120ms
		>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 ≤ 180 ms
		> 180 ms
18 to 35 years	Males and Females	≤ 120 ms
		> 120 ms to ≤ 220 ms
		> 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 ≤140bpm
		> 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 ≤120bpm
		> 120 bpm to ≤ 150 bpm
		> 150 bpm Increase or decrease from baseline >10 bpm Increase or decrease from baseline > 20 bpm
12 to <18years	Males and Females	< 50 bpm
		≥50 bpm to ≤100bpm
		> 100 bpm to ≤ 150 bpm
		> 150 bpm Increase or decrease from baseline >10 bpm Increase or decrease from baseline > 20 bpm
18-35 years	Males and Females	< 50 bpm
		≥50 bpm to ≤100bpm
		> 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 regimen 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 regimen and visitwill 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 for Part 1 Cohort A was estimated under the assumption that adding ZX008 at 0.8 mg/kg/day to current therapy will lead to a mean decrease in drop seizures that is 30 percentage points greater than adding placebo to current therapy. For example, if adding placebo leads to a 10% decrease in seizures, then adding the high dose of ZX008 would be expected to decrease seizures by at least 40%.The variability expected in the trial was estimated from a Phase 3 trial of clobazam for patients with Lennox-Gastaut syndrome (Ng 2011) leading to an assumption that the standard deviation (SD) is 50%. Other assumptions include an allowance for 20% dropouts between randomization and the start of the maintenance period. Under these assumptions, a sample size of 63 subjects per treatment group for a nonparametric analysis affords 90% power to detect a difference between the ZX008 0.8 mg/kg/day and placebo groups that is significant at the $\alpha=0.05$ level. Assuming a 20% drop-out rate prior to the start of the maintenance period yields a requirement for an additional 14 subjects per group for a total of 79 subjects per treatment group for a nonparametric analysis. Similar calculations for the 0.2 mg/kg/day ZX008 group lead to a total required sample size of 237. The number of subjects randomized into Part 1 Cohort A is estimated to be approximately 250 due to the long baseline period.

No formal sample size calculations were conducted related to cardiac safety for Study 1601.

2.5 Randomization and Treatments

Upon completion of the Baseline Period in Part 1, subjects who qualified for the study were randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; 30mg/day maximum [0.2 mg/kg/day or 0.5 mg/kg/day; 20 mg/day maximum for subjects taking concomitant STP]) or placebo. The randomization was stratified by weight (<37.5 kg, ≥37.5 kg) to ensure balance across treatment arms, with a target of at least 25% in each weight group. Subjects were assigned a randomization number by the IWR system upon confirmation that the subject qualified for enrollment in the Titration Period.

3 Cardiac Safety Data Collection and Analysis

3.1 ECG Assessment

3.1.1 Equipment

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

3.1.2 Transfer of ECGs

Electrocardiograms were digitally transferred to ERT for analysis.

3.1.3 Collection of ECGs

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

Single, 12-lead ECGs were collected in Part 1 at:

- Screening (Visit 1)
- Randomization (Visit 3)
- Maintenance Period (Study Day 43, Visit 8)
- EOS/ET (Visit12)
- Follow-up (Visit 14)
- Unscheduled

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

The time of the ECG was not controlled.

3.1.4 Definition of Baseline

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

3.1.5 Variables Measured

At the central laboratory, using CAMI software, 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 (peak 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'sformula (QTcF) will be calculated.

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

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

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

3.1.6 Clinical Analysis of ECGs

The over-reading cardiologist will give a clinical interpretation for each ECG at each time point. These will be presented in the data listing provided at the end of the study. Each ECG will be classified as Normal, 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 transfer test data to ERT. 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 ECHOwas 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

Echocardiograms 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 1 were performed at:

- Screening (Visit 1)
- Maintenance Period (Visit 8; between Study Day 40 and 54)
- EOS/ET (Visit 12;between Study Day 90 and Study Day 113)
- Follow-up (Visit 14)
- Unscheduled

The time of theECHO was not controlled.

3.2.4 Definition of Baseline

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

3.2.5 Variables Measured

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

In addition to assessing each valve (Mitral, Aortic, Tricuspid, and Pulmonary) for regurgitation 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 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'sbetween the two readers was not identical

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/s with orwithout any 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/s
    - 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 ZX008when administered for up to 14 weeks 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 baseline will be calculated and compared for the 0.2 and 0.8 mg/kg/day treatment groups to placebo. The primary outcome is the assessment for the development of valvular heart disease and pulmonary arterial hypertension.

Continuous variables will be summarized using descriptive statistics (i.e., total number, 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.

Categorical variables will be presented as category counts and percentages. Percentages will be presented to onedecimal place.

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

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

4.2 Analysis Set

ECG and ECHO data will be analyzed using the Safety Population, including all randomized subjects who received at least one dose of study medication. The analyses will be based on the actual treatment taken.

No comparisons between sites will beconducted.

4.2.1 Handling of Missing Data

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

4.3 Interim Analysis

No interim analysis is planned for this study.

4.4 Multiplicity Adjustments

No adjustments for multiplicity will be made for the cardiovascular endpoints.

4.5 Primary Analyses

4.5.1 Electrocardiogram

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

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

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

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

4.5.2 Echocardiogram

The primary ECHO objective is to evaluate the effect of ZX008 0.8 mg/kg/day (max 30 mg/day) on the mitral and aortic valves, and in particular evaluating for the development of VHD and PAH.

The number and percentage of subjects with each category of valvular regurgitation will be calculated by regimen and visit for each valve (Mitral, Aortic, Tricuspid, and Pulmonary), based on age (where appropriate), i.e. ≤ 18 years of age and > 18 years of age, 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 and 15 mmHg differences. Abnormal values will be categorized by regimen and visit.

4.6 Secondary Analyses

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

4.7 Additional Analysis

Additional analysis may be used, as appropriate.

4.8 Categorical Analysis

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

5 Tables, Figures, and Listings

Table 1.1.1 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Males and Females, 2 to <12 Years – Cohort A

Table 1.1.2 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Males, 12 to <18Years – Cohort A

Table 1.1.3 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Males, 18 to 35 Years – Cohort A

Table 1.1.4 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Females, 12 to <18Years – Cohort A

Table 1.1.5 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QTcF, Safety Population - Females, 18 to 35 Years – Cohort A

Table 1.2.1 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - Heart Rate, Safety Population - Males and Females, 2 to < 6 Years – Cohort A

Table 1.2.2 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - Heart Rate, Safety Population - Males and Females, 6 to < 12 Years – Cohort A

Table 1.2.3 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - Heart Rate, Safety Population - Males and Females, 12 to <18Years – Cohort A

Table 1.2.4 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - Heart Rate, Safety Population - Males and Females, 18 to 35 Years – Cohort A

Table 1.3.1 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QRS Duration, Safety Population - Males and Females, 2 to < 6 Years – Cohort A

Table 1.3.2 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QRS Duration, Safety Population - Males and Females, 6 to < 12 Years – Cohort A

Table 1.3.3 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QRS Duration, Safety Population - Males and Females, 12 to <18 Years – Cohort A

Table 1.3.4 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - QRS Duration, Safety Population - Males and Females, 18 to 35 Years – Cohort A

Table 1.4.1 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - PR-Interval, Safety Population - Males and Females, 2 to < 6 Years – Cohort A

Table 1.4.2 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - PR-Interval, Safety Population - Males and Females, 6 to < 12 Years – Cohort A

Table 1.4.3 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - PR-Interval, Safety Population - Males and Females, 12 to <18 Years – Cohort A

Table 1.4.4 Means, Mean Differences from Baseline and Upper Bound of One-Sided 95% CI from ANOVA for ECG Data - PR-Interval, Safety Population - Males and Females, 18 to 35 Years – Cohort A

Table 1.5 Means and Mean Differences from Baseline for ECHO Data - PASP, Safety Population – Cohort A

Table 2.1.1 Categorical Summary of ECG Data - QTcF, Safety Population - Males and Females, 2 to <12 Years – Cohort A

Table 2.1.2 Categorical Summary of ECG Data - QTcF, Safety Population - Males, 12 to <18 Years – Cohort A

Table 2.1.3 Categorical Summary of ECG Data - QTcF, Safety Population - Males, 18 to 35 Years – Cohort A

Table 2.1.4 Categorical Summary of ECG Data - QTcF, Safety Population - Females, 12 to <18Years – Cohort A

Table 2.1.5 Categorical Summary of ECG Data - QTcF, Safety Population - Females, 18 to 35 Years – Cohort A

Table 2.1.6 Categorical Summary for ECG Data - QTcF Change from Baseline, Safety Population - Males and Females, 2 to <12 Years – Cohort A

Table 2.1.7 Categorical Summary for ECG Data - QTcF Change from Baseline, Safety Population - Males, 12 to <18Years – Cohort A

Table 2.1.8 Categorical Summary for ECG Data - QTcF Change from Baseline, Safety Population - Males, 18 to 35 Years – Cohort A

Table 2.1.9 Categorical Summary for ECG Data - QTcF Change from Baseline, Safety Population - Females, 12 to <18 Years – Cohort A

Table 2.1.10 Categorical Summary for ECG Data - QTcF Change from Baseline, Safety Population - Females, 18 to 35 Years – Cohort A

Table 2.2.1 Categorical Summary of ECG Data - Heart Rate, Safety Population - Males and Females, 2 to <6 Years – Cohort A

Table 2.2.2 Categorical Summary of ECG Data - Heart Rate, Safety Population - Males and Females, 6 to < 12 Years – Cohort A

Table 2.2.3 Categorical Summary of ECG Data - Heart Rate, Safety Population - Males and Females, 12 to <18Years – Cohort A

Table 2.2.4 Categorical Summary of ECG Data - Heart Rate, Safety Population - Males and Females, 18 to 35 Years – Cohort A

Table 2.2.5 Categorical Summary of ECG Data - Heart Rate Change from Baseline, Safety Population - Males and Females, 2 to <6 Years – Cohort A

Table 2.2.6 Categorical Summary of ECG Data - Heart Rate Change from Baseline, Safety Population - Males and Females, 6 to < 12 Years – Cohort A

Table 2.2.7 Categorical Summary of ECG Data - Heart Rate Change from Baseline, Safety Population - Males and Females, 12 to <18 Years – Cohort A

Table 2.2.8 Categorical Summary of ECG Data - Heart Rate Change from Baseline, Safety Population - Males and Females, 18 to 35 Years – Cohort A

Table 2.3.1 Categorical Summary of ECG Data - QRS Duration, Safety Population - Males and Females, 2 to < 6 Years – Cohort A

Table 2.3.2 Categorical Summary of ECG Data - QRS Duration, Safety Population - Males and Females, 6 to < 12 Years – Cohort A

Table 2.3.3 Categorical Summary of ECG Data - QRS Duration, Safety Population - Males and Females, 12 to <18 Years – Cohort A

Table 2.3.4 Categorical Summary of ECG Data - QRS Duration, Safety Population - Males and Females, 18 to 35 Years – Cohort A

Table 2.4.1 Categorical Summary of ECG Data - PR-Interval, Safety Population - Males and Females, 2 to < 6 Years – Cohort A

Table 2.4.2 Categorical Summary of ECG Data - PR-Interval, Safety Population - Males and Females, 6 to < 12 Years – Cohort A

Listing 2.2 Echo Data at Screening and Rescreening by Subject and Visit, Safety Population – Subjects with Rescreening ECHO Data - Cohort A

6 References

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ZX008-1601: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. 29 July 2019 (Protocol Amendment 2.1).

Project /Protocol No.	Zogenix Limited International, Inc.; Protocol No.: ZX008-1601
Date:	31-June-2021
RE:	Post-Hoc Analyses for Study ZX008-1601 Cohort A – Part 1

APPROVALS	
Syneos Health	
[redacted]	*Electronically signed by:* [redacted] *Reason: I am the author Date: Jul 1, 2021 17:20 EDT*
Lead Biostatistician [redacted]	**Date (dd-Mmm-yyyy)**
Principal Biostatistician [redacted]	*E tronically signed by:* [redacted] *Reason: I am the approver Date: Jul 1, 2021 21:42 EDT*
Senior Reviewing Biostatistician [redacted]	**Date (dd-Mmm-yyyy)**

Zogenix International Limited

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 26-Jul-2021 | 08:07 PDT
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[redacted] **Date (dd-Mmm-yyyy)**

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 23-Jul-2021 | 12:56 PDT
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23-Jul-2021 | 12:56 PDT

[redacted] Statistician on Behalf of Zogenix International Limited **Date (dd-Mmm-yyyy)**

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I have reviewed this document
Signing Time: 23-Jul-2021 | 11:28 PDT
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23-Jul-2021 | 11:28 PDT

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1. Glossary of Abbreviations

Abbreviation	Description
GTC	generalized tonic-clonic seizures
SGTC	Secondarily Generalized Tonic-Clonic seizures
ESC	Epilepsy Study Consortium
ANCOVA	Analysis of Covariance
ILAE	International League Against Epilepsy
mITT	modified Intent-to-Treat
PP	Per Protocol
DCR	Data Change Request
T+M	Titration + Maintenance
M	Maintenance
SAP	Statistical Analysis Plan
VABS	Vineland Adaptive Behavior Scale

2. Purpose

The purpose of this SAP addendum is to document the analyses completed in Part 1 Cohort A that were modified from the Statistical Analysis Plan (SAP) or were not described in the SAP Version 2.0 dated 08JAN2020. An updated table of contents of analyses of the tables, listings, and figures is provided in this addendum.

3. Medication Analyses

Medications were collected on the "Prior Antiepileptic Drugs", "Concomitant Medications", or "Rescue Medications" eCRF pages. Medication start and stop dates were only collected on the Concomitant Medications eCRF pages. Prior medications (ie, non-antiepileptic and non-concomitant drugs) were derived from the Concomitant Medications eCRF page and therefore only included medications that were stopped during the period from 30 days prior to the screening date to the day before first date of study treatment. This was incorporated into Cohort A outputs Table 14.1.4.1.1 and Listing 16.2.4.3.1.1. This will also be incorporated into Table 14.1.4.1.2 and Listing 16.2.4.3.1.2 for Cohort B.

4. New Efficacy Analyses

4.1 New Seizure Types

A post-hoc analysis of the emergence of new seizure types will be performed. The summary of this variable will be based on the Seizure History eCRF (a form that lists both previous and current seizure types experienced by each subject), seizures reported on the seizure diary prior the start of study treatment, and seizures reported during the Titration and Maintenance (T+M) Period of Part 1. Each

subject's unique seizure types experienced prior to study treatment will be determined from the following types:

Seizures Types
Generalized Tonic-Clonic (GTC)
Secondarily Generalized Tonic-Clonic (SGTC)
Tonic
Atonic
Tonic/Atonic
Clonic
Hemiclonic L Body
Hemiclonic R Body
Hemiclonic with Independent L and R
Focal with clear observable signs
Focal without clear observable signs
Myoclonic
Absence/atypical absence
Infantile Spasms
Epileptic Spasms
Other

Subjects with emergence of at least one new seizure type during the T+M Period will be summarized by randomized treatment group. A new seizure type is defined as a seizure type recorded in the seizure diary that was not recorded in the Seizure History eCRF as occurring before the first study drug dose date and that also did not occur during the Baseline Period.

4.2 All Countable Seizures that did not Result in Drops (ESC Confirmed)

The SAP v2.0 08Jan2020 describes increasingly broad groupings of seizure types for efficacy analyses, from the primary endpoint (drop seizures only) to all countable (motor + non-motor) seizures, however it does not describe a seizure grouping that does not include drop seizures. The calculation of the change in the frequency of all countable seizures that did not result in drops (ESC Confirmed) between baseline and the T+M period will be completed similarly to the method described for the primary endpoint. All approved seizures recorded from the diary, which were of a type not listed as an ESC Confirmed Drop seizure, will be included. Similarly, a change in the frequency between baseline and the M period will be determined.

The same non-parametric and parametric Analysis of Covariance (ANCOVA) models described for the primary endpoint will be used for the analyses of all countable seizures that did not result in drops. The mITT and PP population will be used for this analysis.

The number and percentage of subjects who had a worsening, 0% reduction, ≥25% reduction, ≥50% reduction, ≥75% reduction, 100% reduction, and near seizure freedom in the frequency of all countable seizures that did not result in a drop (ESC Confirmed) between Baseline and T+M and between Baseline and M will be summarized by treatment group and overall.

4.3 Sensitivity Analysis of Cluster Imputation

This analysis is an alternative method for imputation of the number of seizure events associated with episodes that were described in the diary as "A cluster of seizures back to back". Refer to section 8.2.1 of the Part 1 SAP for the primary analysis. The "A cluster of seizure back to back" episodes 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 was defined.

1.) Cluster cluster episodes described in the diary as "A cluster of seizures back to back" were 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 were 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 was 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 was 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 was 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 was determined for all discrete cluster episodes in the Short, Medium, and Long discrete cluster duration categories in the population. The median value was then imputed into the Short, Medium, and Long duration back-to-back cluster categories.

The frequency of ESC Confirmed Drop seizures was then determined using the alternative cluster event imputation. The summary statistics, nonparametric model, and parametric models as used for the primary endpoint, were used for the cluster event sensitivity analysis.

4.4 Pre-Data Change Request (DCR) Analyses

A pre-edited version of the seizure datasets 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:

- 2) any edits made through the Trial Manager portal or directly on the device itself were removed,
- 3) 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).

Using the three different versions of the pre-DCR seizure dataset, the seizure frequency rates were reproduced with each set. The following sensitivity analyses were completed using these sets.

<u>ESC Confirmed Drop Seizures</u>

- Summary statistics for observed rate, change from baseline, and percentage change from baseline in rate for the T+M period, M period, up to 2 weeks, up to 6 weeks, up to 10 weeks, and up to 14 weeks. This analysis was completed for the mITT Population
- Summary statistics for observed rate, change from baseline, and percentage change from baseline in rate for the T+M period, M period, up to 2 weeks, up to 6 weeks, up to 10 weeks, and up to 14 weeks using the cluster sensitivity values. This analysis was completed for the mITTPopulation.
- Nonparametric analysis for the T+M period and M period using the original values and alternative cluster imputation method. This analysis was completed for the mITTPopulation.
- Imputation methods for dropouts described in section 8.2.3 of the Part 1 SAP
- Wilcoxon rank-sum test, including Hodges-Lehmann confidence interval for differences from Placebo, described in section 8.2.3 of the Part 1 SAP
- The number and percentage of subjects who had a worsening, 0% reduction, ≥25% reduction, ≥50% reduction, ≥75% reduction, 100% reduction, and near seizure freedom in the frequency of all countable seizures that did not result in a drop (ESC Confirmed) between Baseline and T+M and between Baseline and M will be summarized by treatment group and overall.

- Cumulative response curve for percent of subjects experiencing various % reductions in seizures (mITT Population)
- Summary statistics for observed rate, change from baseline, and percentage change from baseline in rate for the T+M and M period by individual seizure type. This analysis was completed for the mITT Population
- The number and percentage of subjects who had a worsening, 0% reduction, ≥25% reduction, ≥50% reduction, ≥75% reduction, 100% reduction, and near seizure freedom in the frequency of of each individual seizure type between Baseline and T+M and between Baseline and M will be summarized by treatment group and overall. This analysis was completed for the mITT Population.

Seizures that Typically Result in Drops

- Summary statistics for observed rate, change from baseline, and percentage change from baseline in rate for the T+M period, M period, up to 2 weeks, up to 6 weeks, up to 10 weeks, and up to 14 weeks. This analysis was completed for the mITTPopulation.
- Summary statistics for observed rate, change from baseline, and percentage change from baseline in rate for the T+M period, M period, up to 2 weeks, up to 6 weeks, up to 10 weeks, and up to 14 weeks using the cluster sensitivity values. This analysis was completed for the mITTPopulation.
- Nonparametric analysis for the T+M period and M period using the original values and alternative cluster imputation method. This analysis was completed for the mITTPopulation
- Wilcoxon rank-sum test, including Hodges-Lehmann confidence interval for differences from Placebo, described in section 8.2.3 of the Part 1 SAP
- The number and percentage of subjects who had a worsening, 0% reduction, ≥25% reduction, ≥50% reduction, ≥75% reduction, 100% reduction, and near seizure freedom in the frequency of of seizures that typically result in drops between Baseline and T+M and between Baseline and M will be summarized by treatment group and overall. This analysis was completed for the mITT Population.
- Cumulative response curve for percent of subjects experiencing various % reductions in seizures (mITT Population)
- Summary statistics for observed rate, change from baseline, and percentage change from baseline in rate for the T+M and M period by individual seizure type. This analysis was completed for the mITT Population
- The number and percentage of subjects who had a worsening, 0% reduction, ≥25% reduction, ≥50% reduction, ≥75% reduction, 100% reduction, and near seizure freedom in the frequency of of each individual seizure type between Baseline and T+M and between Baseline and M will be summarized by treatment group and overall. This analysis was completed for the mITT Population.

4.5 ESC Confirmed Drop Seizures – Sensitivity to the Supplementary Drop Seizure File

After the Part 1 Cohort A database lock occurred, an updated version of the supplementary drop seizure file, which lists each seizure type per subject that was reconciled to be an ESC Confirmed Drop seizure, was provided that contained corrections to the reconciliation based on findings discovered after database lock. The updated file was used to create a new version of the frequencies of ESC Confirmed drop seizures, and the same analyses used for the primary analyses of ESC Confirmed Drop seizures were applied to this data. The analysis outputs were used to confirm that no changes to study conclusions were changed as a result of the above-mentioned findings; they were not used to replace original data.

4.6 Sensitivity Analysis of Status Epilepticus

A sensitivity analysis of status epilepticus cases determined from the seizure diary was conducted, based on seizure types officially recognized as status epilepticus by the International League Against Epilepsy (ILAE). Seizure events with duration > 10 minutes that were of one of the following types were identified.

- Absence or atypical absence
- Absence/atypical absence
- Focal with clear observable motor signs
- Focal with clear observable signs
- Focal without clear observable motor signs
- Generalized tonic-clonic
- Secondarily generalized tonic-clonic

Such events were further divided in order of increasing risk/emergency, ie, into those events that required

- No Rescue Medications
- 1 Rescue Medications
- > 1 Rescue Medications

The number of events of each type was counted in the Baseline Period, T+M Period, and M Period as well as the rate (events/ 28 days) was determined. The number of subjects with at least one event was summarized and the incidence rate between the active treatment group and the placebo group was compared using a Fisher's Exact Test.

4.7 Vineland Adaptive Behavior Scale (VABS)

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.

5. Table of Contents of Outputs for Part 1

The following shows the current table of contents of the outputs for Part 1. Note that tables, figures or listings with an "s", "b", or "c" will have structure identical to the corresponding table, listing, figure without the extra letter. The extra letter indicates whether the output was a sensitivity analysis, Pre-DCR Version 2, or Pre-DCR Version 3 output, respectively.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
	14.1	**Demographic data and other baseline characteristics**	
	14.1.1	**Subject disposition**	
Table	14.1.1.1.1	Overall Subject Disposition in Part 1 (Cohort A – North America, Europe, Australia) – All Enrolled Subjects	
Table	14.1.1.1.2	Overall Subject Disposition in Part 1 (Cohort B - Japan) – All Enrolled Subjects	
Table	14.1.1.2.1	Major Protocol Deviations in Part 1 (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.1.1.2.2	Major Protocol Deviations in Part 1 (Cohort B - Japan) – Safety Population	
Table	14.1.1.3.1	Study Populations in Part 1 (Cohort A – North America, Europe, Australia)	
Table	14.1.1.3.2	Study Populations in Part 1 (Cohort B - Japan)	
	14.1.2	**Demographic and other baseline characteristics**	
Table	14.1.2.1.1	Demographic and Baseline Characteristics (Cohort A – North America, Europe, Australia) – Safety Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.1.2.1.2	Demographic and Baseline Characteristics (Cohort B - Japan) – Safety Population	
Table	14.1.2.2.1	Demographic and Baseline Characteristics (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.1.2.2.2	Demographic and Baseline Characteristics (Cohort B - Japan) – mITT Population	
	14.1.3	**Medical history**	
Table	14.1.3.1.1	Medical and Neurologic History (Cohort A – North America, Europe, Australia) – Safety Population	Title Change; Neurologic History included in this table.
Table	14.1.3.1.2	Medical and Neurologic History (Cohort B – Japan) – Safety Population	Title Change; Neurologic History included in this table.
	14.1.4	**Prior and concomitant medication/treatment**	
Table	14.1.4.1.1	Medications and Therapies/Treatments Stopped during or up to 30 Days prior to Screening (Cohort A – North America, Europe, Australia) – Safety Population	Title Changed. Only medications that had stopped during screening or up to and including 30 days prior to the screening were included.
Table	14.1.4.1.2	Medications and Therapies/Treatments Stopped during or up to 30 Days prior to Screening (Cohort B – Japan) – Safety Population	Title Changed. Only medications that had stopped during screening or up to and including 30 days prior to the screening were included.
Table	14.1.4.2.1	Concomitant Medications and Therapies/Treatments in Part 1 (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.1.4.2.2	Concomitant Medications and Therapies/Treatments in Part 1 (Cohort B – Japan) – Safety Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.1.4.3.1	Prior Antiepileptic Treatment (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.1.4.3.2	Prior Antiepileptic Treatment (Cohort B – Japan) – Safety Population	
Table	14.1.4.4.1.1	Concomitant Antiepileptic Treatment in Part 1 (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.1.4.4.1.2	Concomitant Antiepileptic Treatment in Part 1 (Cohort B – Japan) - Safety Population	
Table	14.1.4.4.2.1	Rescue Medications in Part 1 (Cohort A – North America, Europe, Australia) – Safety Population	Title Change from Concomitant Rescue Medications
Table	14.1.4.4.2.2	Rescue Medications in Part 1 (Cohort B – Japan) - Safety Population	Title Change from Concomitant Rescue Medications
	14.1.5	**Treatment Exposure and compliance**	
Table	14.1.5.1.1	Duration of IMP Treatment Exposure in Part 1 (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.1.5.1.2	Duration of IMP Treatment Exposure in Part 1 (Cohort B – Japan) – Safety Population	
Table	14.1.5.2.1.1	Compliance to IMP intake in Part 1 (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.1.5.2.1.2	Compliance to IMP intake in Part 1 (Cohort B – Japan) - mITT Population	
Table	14.1.5.2.2.1	Compliance to IMP intake in Part 1 (Cohort A – North America, Europe, Australia) - Safety Population	This table was described in the shells, but was not included in the table of contents.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.1.5.2.2.2	Compliance to IMP intake in Part 1 (Cohort B – Japan) - Safety Population	This table was described in the shells, but was not included in the table of contents.
Table	14.1.5.2.3.1	Compliance to IMP Intake in Part 1 based on Bottle Weight (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.1.5.2.3.2	Compliance to IMP Intake in Part 1 based on Bottle Weight (Cohort B – Japan) - mITT Population	
Table	14.1.5.2.4.1	Compliance to IMP Intake in Part 1 based on Bottle Weight (Cohort A – North America, Europe, Australia) - Safety Population	This table was described in the shells, but was not included in the table of contents.
Table	14.1.5.2.4.2	Compliance to IMP Intake in Part 1 based on Bottle Weight (Cohort B – Japan) - Safety Population	This table was described in the shells, but was not included in the table of contents.
	14.2	**Efficacy, pharmacokinetics, and pharmacodynamics**	
	14.2.1	**Efficacy – ZX008 0.8 and 0.2 mg/kg/day vs Placebo** **Seizures resulting in drops**	
Table	14.2.1.1.1.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.1.1.1.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplementary Seizure File updated post-Part 1 Database Lock.
Table	14.2.1.1.1.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort A –	New Table using Pre-DCR dataset Version 2

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	
Table	14.2.1.1.1.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3
Table	14.2.1.1.1.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – mITT Population	Table number clarified in shells.
Table	14.2.1.1.1.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cluster Event Sensitivity Analysis) (Cohort A – North America, Europe, Australia) – mITT Population	Post-hoc table addition. The shell used is the same as 14.2.1.1.1.1. The different methodology of imputing the number of seizure events associated with Cluster events was added.
Table	14.2.1.1.1.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cluster Event Sensitivity Analysis) (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplementary Seizure File updated post-Part 1 Database Lock
Table	14.2.1.1.1.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cluster Event Sensitivity Analysis) (Cohort B – Japan) – mITT Population	Post-hoc table addition. The shell used is the same as 14.2.1.1.1.1. The different methodology of imputing the number of seizure events associated with Cluster events was added.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.1.2.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.1.1.2.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – PP Population	New Table using Supplementary Seizure File updated post-Part 1 Database Lock
Table	14.2.1.1.2.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – PP Population	
Table	14.2.1.2.1.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	Table Number Update
Table	14.2.1.2.1.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplementary Seizure File updated post-Part 1 Database Lock
Table	14.2.1.2.1.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2
Table	14.2.1.2.1.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.2.1.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	Planned table per SAP. This Table number was added to the Table of Contents.
Table	14.2.1.2.1.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort A – North America, Europe, Australia)- MITT Population	Table was described in the SAP, but shell had not been produced. This was added to the shells.
Table	14.2.1.2.1.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort A – North America, Europe, Australia)- MITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.2.1.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort B – Japan)- MITT Population	Table was described in the SAP, but shell had not been produced. This was added to the shells.
Table	14.2.1.2.2.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	Table Number Update
Table	14.2.1.2.2.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.2.2.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	Planned table per SAP. This Table number was added to the Table of Contents.
Table	14.2.1.3.1.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	Table Number Update
Table	14.2.1.3.1.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.3.1.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population	Planned table per SAP. This Table number was added to the Table of Contents.
Table	14.2.1.3.1.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort A – North America, Europe, Australia) – mITT Population	Table was described in the SAP, but shell had not been produced. This was added to the shells.
Table	14.2.1.3.1.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.3.1.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort B – Japan) – mITT Population	Table was described in the SAP, but shell had not been produced. This was added to the shells.
Table	14.2.1.3.2.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	Table Number Update
Table	14.2.1.3.2.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.3.2.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	Added to the Table of Contents
Table	14.2.1.4.1.1	Percent Improvement in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.1.4.1.1s	Sensitivity Analysis of Percent Improvement in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.4.1.1b	Percent Improvement in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)	New Table using Pre-DCR dataset Version 2

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		(Pre-DCR Seizure Event Dataset Version 2) – mITT Population	
Table	14.2.1.4.1.1c	Percent Improvement in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3
Table	14.2.1.4.1.2	Percent Improvement in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort B – Japan) – mITT Population	
Table	14.2.1.4.2.1	Percent Improvement in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.1.4.2.1s	Sensitivity Analysis of Percent Improvement in Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – PP Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.4.2.2	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort B – Japan) – mITT Population	
Figure	14.2.1.5.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort A – North America, Europe, Australia) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Figure	14.2.1.5.1.1s	Sensitivity Analysis of Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort A – North America, Europe, Australia) – mITT Population	New Figure using Supplemental Seizure File updated post-Part 1 Database Lock
Figure	14.2.1.5.1.1b	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Figure using Pre-DCR dataset Version 2
Figure	14.2.1.5.1.1c	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Figure using Pre-DCR dataset Version 3
Figure	14.2.1.5.1.2	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort B - Japan) – mITT Population	
Table	14.2.1.6.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Age Subgroup: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.2.1.6.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Age Subgroup: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.6.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Sex: Nonparametric Analysis – (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.2.1.6.2s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Sex: Nonparametric Analysis – (Cohort A – North America, Europe, Australia) - mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.6.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Weight Subgroup: Nonparametric Analysis – (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.2.1.6.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Weight Subgroup: Nonparametric Analysis – (Cohort A – North America, Europe, Australia) - mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.6.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Number of Concomitant Antiepileptic Medications Used: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.2.1.6.4s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Number of Concomitant Antiepileptic Medications Used: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.6.5	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Number of Prior Antiepileptic Medications Used: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.2.1.6.5s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Number of Prior Antiepileptic Medications Used: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.6.6	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Baseline Frequency of Seizures that Result in Drops: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.2.1.6.6s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Baseline Frequency of Seizures that Result in Drops: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.6.7	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Race Group: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	New Table requested.
Table	14.2.1.6.8	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Geographic Region: Nonparametric Analysis (Cohort A – North America, Europe, Australia) mITT Population	New Table requested.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.7.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 1 (Worst Value Substituted for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.1.7.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 1 (Worst Value Substituted for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.7.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 1 (Worst Value Substituted for Dropouts) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2
Table	14.2.1.7.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 1 (Worst Value Substituted for Dropouts) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3
Table	14.2.1.7.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 1 (Worst Value Substituted for Dropouts) (Cohort B – Japan)– mITT Population	Correction of Table Title for Cohort B

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.7.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 2 (Differential Imputation Method for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population	Correction of Table Title for Cohort A
Table	14.2.1.7.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 2 (Differential Imputation Method for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.7.3b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 2 (Differential Imputation Method for Dropouts) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2
Table	14.2.1.7.3c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 2 (Differential Imputation Method for Dropouts) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3
Table	14.2.1.7.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity Analysis 2 (Differential Imputation Method for Dropouts) (Cohort B – Japan) – mITT Population	Correction of Table Title for Cohort B

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.8.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Wilcoxon Analysis – Sensitivity to Analysis Method (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.1.8.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Wilcoxon Analysis – Sensitivity to Analysis Method (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.8.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Wilcoxon Analysis – Sensitivity to Analysis Method (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2
Table	14.2.1.8.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Wilcoxon Analysis – Sensitivity to Analysis Method (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3
Table	14.2.1.8.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Wilcoxon Analysis – Sensitivity to Analysis Method (Cohort B – Japan) – mITT Population	
Table	14.2.1.9.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort A – North America, Europe, Australia) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.9.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.9.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2
Table	14.2.1.9.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3
Table	14.2.1.9.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort B – Japan) – mITT Population	
Table	14.2.1.10.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.1.10.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.1.10.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2
Table	14.2.1.10.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3
Table	14.2.1.10.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort B – Japan) – mITT Population	
Table	14.2.1.10.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort A – North America, Europe, Australia) – mITT Population	Sensitivity Analysis to assess the impact of imputation of number of events associated with cluster events.
Table	14.2.1.10.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.1.10.3b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort A – North America,	New Table using Pre-DCR dataset Version 2

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	
Table	14.2.1.10.3c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3
Table	14.2.1.10.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort B – Japan) – mITT Population	Sensitivity Analysis to assess the impact of imputation of number of events associated with cluster events.
	14.2.2	**Efficacy – Clinical Global Impression – Improvement rating by Parent/Caregiver and Investigator**	
Table	14.2.2.1.1.1	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 (Cohort A – North America, Europe, Australia) – mITT Population	Table Title adjustment to align with shell.
Table	14.2.2.1.1.2	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 (Cohort B – Japan) – mITT Population	Table Title adjustment to align with shell.
Table	14.2.2.1.2.1	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 (Cohort A – North America, Europe, Australia) – PP Population	Table Title adjustment to align with shell.
Table	14.2.2.1.2.2	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 (Cohort B – Japan) – PP Population	Table Title adjustment to align with shell.
Table	14.2.2.1.3.1	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 by Age Subgroup (Cohort A – North America, Europe, Australia) – mITT Population	Table Title adjustment to align with shell.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.2.1.3.2	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 by Sex (Cohort A – North America, Europe, Australia) – mITT Population	Table Title adjustment to align with shell.
Table	14.2.2.1.3.3	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 by Weight Subgroup (Cohort A – North America, Europe, Australia) – mITT Population	Table Title adjustment to align with shell.
Table	14.2.2.1.3.4	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 by Number of Concomitant Antiepileptic Medications Used (Cohort A – North America, Europe, Australia) – mITT Population	Table Title adjustment to align with shell.
Table	14.2.2.1.3.5	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 by Number of Prior Antiepileptic Medications Used (Cohort A – North America, Europe, Australia) – mITT Population	Table Title adjustment to align with shell.
Table	14.2.2.1.3.6	Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 by Baseline Frequency of Seizures that Result in Drops (Cohort A – North America, Europe, Australia) – mITT Population	Table Title adjustment to align with shell.
Table	14.2.2.1.3.6s	Sensitivity Analysis of Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 by Baseline Frequency of Seizures that Result in Drops (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Figure	14.2.2.2.1	Distribution of Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 (Cohort A – North America, Europe, Australia)– mITT Population	Figure Title adjustment to align with shell.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Figure	14.2.2.2.2	Distribution of Clinical Global Impression – Improvement (CGI-I) Rating by Investigator in Part 1 (Cohort B – Japan) – mITT Population	Figure Title adjustment to align with shell.
	14.2.3	**Countable Motor Seizures**	
Table	14.2.3.1.1.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.3.1.1.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – mITT Population	
Table	14.2.3.1.2.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.3.1.2.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – PP Population	
Table	14.2.3.2.1.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.3.2.1.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	
Table	14.2.3.2.2.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.3.2.2.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	
Table	14.2.3.3.1.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia)– mITT Population	
Table	14.2.3.3.1.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population	
Table	14.2.3.3.2.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.3.3.2.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	
Table	14.2.3.4.1.1	Percent Improvement in Frequency of Countable Motor Seizures per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	
Table	14.2.3.4.1.2	Percent Improvement in Frequency of Countable Motor Seizures per 28 days during Part 1: Logistic Regression (Cohort B – Japan) – mITT Population	
Figure	14.2.3.5.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Countable Motor Seizures during Part 1 (Cohort A – North America, Europe, Australia)– mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Figure	14.2.3.5.1.2	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Countable Motor Seizures during Part 1 (Cohort B – Japan)– mITT Population	
	14.2.4.1	**Efficacy – Typical Drop Seizures**	
Table	14.2.4.1.1.1.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	Title update made at the request of Zogenix
Table	14.2.4.1.1.1.1s	Sensitivity Analysis of Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.4.1.1.1.1b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2
Table	14.2.4.1.1.1.1c	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3
Table	14.2.4.1.1.1.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – mITT Population	Title update made at the request of Zogenix
Table	14.2.4.1.1.2.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – PP Population	Title update made at the request of Zogenix

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.1.1.2.1b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – PP Population	New Table using Pre-DCR dataset Version 2
Table	14.2.4.1.1.2.1c	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – PP Population	New Table using Pre-DCR dataset Version 3
Table	14.2.4.1.1.2.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – PP Population	Title update made at the request of Zogenix
Table	14.2.4.1.1.2.2b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort B – Japan) (Pre-DCR Seizure Event Dataset Version 2) – PP Population	New Table using Pre-DCR dataset Version 2
Table	14.2.4.1.1.2.2c	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Summary Statistics (Cohort B – Japan) (Pre-DCR Seizure Event Dataset Version 3) – PP Population	New Table using Pre-DCR dataset Version 3
Table	14.2.4.1.2.1.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	Title update made at the request of Zogenix
Table	14.2.4.1.2.1.1b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2
Table	14.2.4.1.2.1.1c	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A –	New Table using Pre-DCR dataset Version 3

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	
Table	14.2.4.1.2.1.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	Title update made at the request of Zogenix
Table	14.2.4.1.2.2.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	Title update made at the request of Zogenix
Table	14.2.4.1.2.2.1b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2)– PP Population	New Table using Pre-DCR dataset Version 2
Table	14.2.4.1.2.2.1c	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – PP Population	New Table using Pre-DCR dataset Version 3
Table	14.2.4.1.2.2.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	Title update made at the request of Zogenix
Table	14.2.4.1.3.1.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	Title update made at the request of Zogenix
Table	14.2.4.1.3.1.1b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.1.3.1.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population	Title update made at the request of Zogenix
Table	14.2.4.1.3.2.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	Title update made at the request of Zogenix
Table	14.2.4.1.3.2.1b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2)– PP Population	New Table using Pre-DCR dataset Version 2
Table	14.2.4.1.3.2.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	Title update made at the request of Zogenix
Table	14.2.4.1.4.1.1	Percent Improvement in Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	Title update made at the request of Zogenix
Table	14.2.4.1.4.1.1b	Percent Improvement in Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population (Pre-DCR Seizure Event Dataset Version 2)	New Table using Pre-DCR dataset Version 2
Table	14.2.4.1.4.1.1c	Percent Improvement in Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population (Pre-DCR Seizure Event Dataset Version 3)	New Table using Pre-DCR dataset Version 3

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.1.4.1.2	Percent Improvement in Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Logistic Regression (Cohort B – Japan)– mITT Population	Title update made at the request of Zogenix
Figure	14.2.4.1.5.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures that Typically Result in Drops during Part 1 (Cohort A – North America, Europe, Australia)– mITT Population	Title update made at the request of Zogenix
Figure	14.2.4.1.5.1.1b	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures that Typically Result in Drops during Part 1 (Cohort A – North America, Europe, Australia)– mITT Population (Pre-DCR Seizure Event Dataset Version 2)	New Figure using Pre-DCR dataset Version 2
Figure	14.2.4.1.5.1.1c	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures that Typically Result in Drops during Part 1 (Cohort A – North America, Europe, Australia)– mITT Population (Pre-DCR Seizure Event Dataset Version 3)	New Figure using Pre-DCR dataset Version 3
Figure	14.2.4.1.5.1.2	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures that Typically Result in Drops during Part 1 (Cohort B – Japan)– mITT Population	
Table	14.2.4.1.6.1.1b	Change in Seizures that Typically Result per 28 days in Drops from Baseline during Part 1: Wilcoxon Analysis - Sensitivity to Analysis Method) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - mITT Population	New Figure using Pre-DCR dataset Version 2

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.1.6.1.1c	Change in Seizures that Typically Result per 28 days in Drops from Baseline during Part 1: Wilcoxon Analysis - Sensitivity to Analysis Method) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - mITT Population	New Figure using Pre-DCR dataset Version 3
	14.2.4.2	**Efficacy – Countable Non-Motor Seizures**	
Table	14.2.4.2.1.1.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.4.2.1.1.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – mITT Population	
Table	14.2.4.2.1.2.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.4.2.1.2.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – PP Population	
Table	14.2.4.2.2.1.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.4.2.2.1.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.2.2.2.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.4.2.2.2.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	
Table	14.2.4.2.3.1.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.4.2.3.1.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population	
Table	14.2.4.2.3.2.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.4.2.3.2.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	
Table	14.2.4.2.4.1.1	Percent Improvement in Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	
Table	14.2.4.2.4.1.2	Percent Improvement in Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Logistic Regression (Cohort B – Japan)– mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Figure	14.2.4.2.5.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Countable Non-Motor Seizures during Part 1 (Cohort A – North America, Europe, Australia)– mITT Population	
Figure	14.2.4.2.5.1.2	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Countable Non-Motor Seizures during Part 1 (Cohort B – Japan)– mITT Population	
	14.2.4.3	**Efficacy – All Countable Seizures (Motor + Non-Motor)**	
Table	14.2.4.3.1.1.1	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.4.3.1.1.2	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – mITT Population	
Table	14.2.4.3.1.2.1	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.4.3.1.2.2	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Summary Statistics (Cohort B – Japan) – PP Population	
Table	14.2.4.3.2.1.1	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.3.2.1.2	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	
Table	14.2.4.3.2.2.1	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.4.3.2.2.2	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	
Table	14.2.4.3.3.1.1	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.4.3.3.1.2	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population	
Table	14.2.4.3.3.2.1	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Table	14.2.4.3.3.2.2	Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	
Table	14.2.4.3.4.1.1	Percent Improvement in Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.3.4.1.2	Percent Improvement in Frequency of All Countable Seizures (Motor + Non-Motor) per 28 days during Part 1: Logistic Regression (Cohort B – Japan)	Title correction
Figure	14.2.4.3.5.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in All Countable Seizures (Motor + Non-Motor) during Part 1 (Cohort A – North America, Europe, Australia)– mITT Population	Title correction
Figure	14.2.4.3.5.1.2	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in All Countable Motor Seizures (Motor + Non-Motor) during Part 1 (Cohort B – Japan)– mITT Population	Title correction
Table	14.2.4.4.1.1	Change from Baseline in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) - mITT Population	Table Number Correction; This table was also updated to summarize the seizure types that were typically associated with drop seizures that were classified as ESC Confirmed Drop Seizures.
Table	14.2.4.4.1.1s	Sensitivity Analysis of Change from Baseline in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) - mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock; The only sections affected by the update are the summary of seizure types that were typically associated with drop seizures that were classified as ESC Confirmed Drop Seizures.
Table	14.2.4.4.1.1b	Change from Baseline in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) - mITT Population	New Table using Pre-DCR dataset Version 2. The only sections affected by the DCR update are the summary of seizure types that were typically associated with drop

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
			seizures that were classified as ESC Confirmed Drop Seizures.
Table	14.2.4.4.1.1c	Change from Baseline in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) - mITT Population	New Table using Pre-DCR dataset Version 3. The only sections affected by the DCR update are the summary of seizure types that were typically associated with drop seizures that were classified as ESC Confirmed Drop Seizures.
Table	14.2.4.4.1.2	Change from Baseline in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort B – Japan) – mITT Population	Table Number Correction
Table	14.2.4.4.2.1	Percent Improvement in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	Table Number Correction
Table	14.2.4.4.2.1s	Sensitivity Analysis of Percent Improvement in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock; The only sections affected by the update are the summary of seizure types that were typically associated with drop seizures that were classified as ESC Confirmed Drop Seizures.
Table	14.2.4.4.2.1b	Percent Improvement in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	New Table using Pre-DCR dataset Version 2. The only sections affected by the DCR update are the summary of seizure types that were typically associated with drop seizures that were classified as ESC Confirmed Drop Seizures.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.4.2.1c	Percent Improvement in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	New Table using Pre-DCR dataset Version 3. The only sections affected by the DCR update are the summary of seizure types that were typically associated with drop seizures that were classified as ESC Confirmed Drop Seizures.
Table	14.2.4.4.2.2	Percent Improvement in Seizure Frequency by Types during Part 1: Summary Statistics (Cohort B – Japan) – mITT Population	Table Number Correction
	14.2.4.5	**All Countable Seizures that Did Not Result in Drops (ESC Confirmed)**	
Table	14.2.4.5.1.1.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) - mITT Population	New Post-hoc defined endpoint
Table	14.2.4.5.1.1.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort B – Japan) - mITT Population	New Post-hoc defined endpoint
Table	14.2.4.5.1.2.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) - PP Population	New Post-hoc defined endpoint
Table	14.2.4.5.1.2.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Summary Statistics (Cohort B – Japan) - PP Population	New Post-hoc defined endpoint

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.5.2.1.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	New Post-hoc defined endpoint
Table	14.2.4.5.2.1.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) - mITT Population	New Post-hoc defined endpoint
Table	14.2.4.5.2.2.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - PP Population	New Post-hoc defined endpoint
Table	14.2.4.5.2.2.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) - PP Population	New Post-hoc defined endpoint
Table	14.2.4.5.3.1.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	New Post-hoc defined endpoint
Table	14.2.4.5.3.1.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) - mITT Population	New Post-hoc defined endpoint
Table	14.2.4.5.3.2.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) - PP Population	New Post-hoc defined endpoint

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.5.3.2.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) - PP Population	New Post-hoc defined endpoint
Table	14.2.4.5.4.1.1	Percent Improvement in Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) - mITT Population	New Post-hoc defined endpoint
Table	14.2.4.5.4.1.2	Percent Improvement in Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort B – Japan) - mITT Population	New Post-hoc defined endpoint
Figure	14.2.4.5.5.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in All Countable Seizures that did not Result in Drops (ESC Confirmed) during Part 1 (Cohort A – North America, Europe, Australia) - mITT Population	New Post-hoc defined endpoint
Figure	14.2.4.5.5.1.2	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in All Countable Seizures that did not Result in Drops (ESC Confirmed) during Part 1 (Cohort B – Japan) - mITT Population	New Post-hoc defined endpoint
	14.2.4.6	**New Seizure Types**	
Table	14.2.4.6.1.1	New Seizure Types During Part 1 (Cohort A – North America, Europe, Australia) - mITT Population	New Post-hoc defined endpoint
Table	14.2.4.6.1.2	New Seizure Types During Part 1 (Cohort B – Japan) - mITT Population	New Post-hoc defined endpoint

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.4.7.1.1.1	Frequency of Seizures Resulting in Drops (Caregiver Determination) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) – mITT Population	New Post-hoc defined endpoint
Table	14.2.4.7.2.1.1	Frequency of Seizures Resulting in Drops (Caregiver Determination) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	New Post-hoc defined endpoint
Table	14.2.4.7.4.1.1	Percent Improvement in Frequency of Seizures Resulting in Drops (Caregiver Determination) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	New Post-hoc defined endpoint
Figure	14.2.4.7.5.1.1	Cumulative Response Curve for Percent of Subjects Experiencing Various % Reductions in Seizures Resulting in Drops (Caregiver Determination) during Part 1 (Cohort A – North America, Europe, Australia)– mITT Population	New Post-hoc defined endpoint
	14.2.5	**Efficacy – Seizure-free Days**	
Table	14.2.5.1.1	Number of Seizure Free Days per 28 Days during Part 1: Nonparametric Analysis: (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.2.5.1.2	Number of Seizure Free Days per 28 Days during Part 1: Nonparametric Analysis (Cohort B – Japan) - mITT Population	
Table	14.2.5.2.1	Number of Drop Seizure Free Days per 28 Days (ESC Confirmed) during Part 1: Nonparametric Analysis: (Cohort A – North America, Europe, Australia) - mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.5.2.1s	Sensitivity Analysis of Number of Drop Seizure Free Days per 28 Days (ESC Confirmed) during Part 1: Nonparametric Analysis: (Cohort A – North America, Europe, Australia) - mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.5.2.2	Number of Drop Seizure Free Days per 28 Days (ESC Confirmed) during Part 1: Nonparametric Analysis (Cohort B – Japan) - mITT Population	
	14.2.6	**Efficacy – Duration of the Longest Interval between Seizures Resulting in Drops**	
Table	14.2.6.1	Duration of Longest Interval between Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.6.1s	Sensitivity Analysis of Duration of Longest Interval between Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort A – North America, Europe, Australia) – mITT Population	New Table using Supplemental Seizure File updated post-Part 1 Database Lock
Table	14.2.6.2	Duration of Longest Interval between Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort B – Japan)– mITT Population	
Figure	14.2.6.3	Boxplot of the Duration of Longest Interval between Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort A – North America, Europe, Australia)– mITT Population	
Figure	14.2.6.3s	Sensitivity Analysis of Boxplot of the Duration of Longest Interval between Seizures Resulting in Drops (ESC	New Table using Supplemental Seizure File updated post-Part 1 Database Lock

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		Confirmed) during Part 1 (Cohort A – North America, Europe, Australia)– mITT Population	
Figure	14.2.6.4	Boxplot of the Duration of Longest Interval between Seizures Resulting in Drops (ESC Confirmed) during Part 1 (Cohort B – Japan)– mITT Population	
	14.2.7	**Efficacy – Clinical Global Impression – Improvement rating by Parent/Caregiver**	
Table	14.2.7.1.1	Clinical Global Impression – Improvement Rating by Parent/Caregiver in Part 1 (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.7.1.2	Clinical Global Impression – Improvement Rating by Parent/Caregiver in Part 1 (Cohort B – Japan) – mITT Population	
Figure	14.2.7.2.1	Distribution of Clinical Global Impression – Improvement Rating by Parent/Caregiver in Part 1 (Cohort A – North America, Europe, Australia)– mITT Population	
Figure	14.2.7.2.2	Distribution of Clinical Global Impression – Improvement Rating by Parent/Caregiver in Part 1 (Cohort B – Japan) – mITT Population	
	14.2.8	**Efficacy – Incidence of Status Epilepticus**	
Table	14.2.8.1.1	Number of Episodes of Status Epilepticus (SE) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) - mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.8.1.2	Number of Episodes of Status Epilepticus (SE) per 28 days during Part 1: Summary Statistics (Cohort B – Japan) - mITT Population	
Table	14.2.8.1.3	Sensitivity Analysis of Number of Episodes of Status Epilepticus (SE) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) - mITT Population	New Analysis of Status Epilepticus using the diary events that were generalized tonic/clonic, secondarily generalized tonic/clonic, focal with clear observable signs, focal without clear observable sings, or absence/atypical absence. These events were further separated into those events that required 0 rescue medications, 1 rescue medication, or > 1 rescue medications associated with the seizure event.
Table	14.2.8.1.4	Sensitivity Analysis of Number of Episodes of Status Epilepticus (SE) per 28 days during Part 1: Summary Statistics (Cohort A – North America, Europe, Australia) - mITT Population	New Analysis of Status Epilepticus using the diary events that were generalized tonic/clonic, secondarily generalized tonic/clonic, focal with clear observable signs, focal without clear observable sings, or absence/atypical absence. These events were further separated into those events that required 0 rescue medications, 1 rescue medication, or > 1 rescue medications associated with the seizure event.
Table	14.2.8.2.1	Number of Days where Episodes of Status Epilepticus (SE) Occurred per 28 Days during Part 1: Summary Statistics	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		and Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Table	14.2.8.2.2	Number of Days where Episodes of Status Epilepticus (SE) Occurred per 28 Days during Part 1: Summary Statistics and Nonparametric Analysis (Cohort B – Japan) - mITT Population	
	14.2.9	**Efficacy – Rescue Medication**	
Table	14.2.9.1.1	Days with Rescue Medication Usage in Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.9.1.2	Days with Rescue Medication Usage in Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	
Table	14.2.9.2.1	Number of Rescue Medications Used per Status Epilepticus Episode in Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Table	14.2.9.2.2	Number of Rescue Medications Used per Status Epilepticus Episode in Part 1: Nonparametric Analysis (Cohort B – Japan) - mITT Population	
Table	14.2.9.3.1	Categorical Analysis of Change from Baseline in the Number of Days with Rescue Medication Usage in Part 1 (Cohort A – North America, Europe, Australia) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.9.3.2	Categorical Analysis of Change from Baseline in the Number of Days with Rescue Medication Usage in Part 1 (Cohort B – Japan) – mITT Population	
	14.2.10	**Efficacy – Hospitalization and Resource Utilization for Treatment of Seizures**	
Table	14.2.10.1.1	Hospitalization and Other Healthcare Resource Utilization to Treat Seizure during Study: Summary statistics (Cohort A – North America, Europe, Australia) – mITT Population	Table Title updated.
Table	14.2.10.1.2	Hospitalization and Other Healthcare Resource Utilization to Treat Seizure during Study: Summary statistics (Cohort B – Japan) – mITT Population	Table Title updated.
	14.2.12	**Exploratory Efficacy – Quality of Life in Childhood Epilepsy Scale**	
Table	14.2.12.1.1	Quality of Life in Childhood Epilepsy (QOLCE) in Part 1: Summary Statistics and Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT population	
Table	14.2.12.1.2	Quality of Life in Childhood Epilepsy (QOLCE) in Part 1: Summary Statistics and Nonparametric Analysis (Cohort B – Japan) – mITT population	
	14.2.13	**Exploratory Efficacy – Zarit Caregiver Burden Inventory**	
Table	14.2.13.1.1	Zarit Caregiver Burden Inventory during Part 1: Normal; Borderline Abnormal; and Abnormal Categories (Cohort A – North America, Europe, Australia) – mITT population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.2.13.1.2	Zarit Caregiver Burden Inventory during Part 1: Normal; Borderline Abnormal; and Abnormal Categories (Cohort B – Japan) – mITT population	
Table	14.2.13.2.1	Zarit Caregiver Inventory Index Score during Part 1: Summary Descriptive Statistics (Cohort A – North America, Europe, Australia)– mITT population	
Table	14.2.13.2.2	Zarit Caregiver Inventory Index Score during Part 1: Summary Descriptive Statistics (Cohort B – Japan) – mITT population	
	14.2.14	**Exploratory Efficacy – Parent /Caregiver Ratings using HADS Scale**	
Table	14.2.14.1.1	Parent/Caregiver Ratings Based on Hospital Anxiety and Depression Scale (HADS) during Part 1: Normal; Borderline Abnormal, and Abnormal Categories (Cohort A – North America, Europe, Australia) – mITT population	
Table	14.2.14.1.2	Parent/Caregiver Ratings Based on Hospital Anxiety and Depression Scale (HADS) during Part 1: Normal; Borderline Abnormal, and Abnormal Categories (Cohort B – Japan)– mITT population	
Table	14.2.14.2.1	Parent/Caregiver Ratings Based on Hospital Anxiety and Depression Scale (HADS) during Part 1: Summary Descriptive Statistics (Cohort A – North America, Europe, Australia) -mITT population	
Table	14.2.14.2.2	Parent/Caregiver Ratings Based on Hospital Anxiety and Depression Scale (HADS) during Part 1: Summary Descriptive Statistics (Cohort B – Japan) – mITT population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
	14.3	**Safety**	
	14.3.1	**Summary of adverse events**	
Table	14.3.1.1.1.1	Overview of Number of Subjects with TEAE during Part 1 (Cohort A – North America, Europe, Australia)– Safety Population	
Table	14.3.1.1.1.2	Overview of Number of Subjects with TEAE during Part 1 (Cohort B – Japan) – Safety Population	
Table	14.3.1.2.1.1	Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term (Cohort A – North America, Europe, Australia)– Safety Population	
Table	14.3.1.2.1.2	Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term (Cohort B – Japan) – Safety Population	
Table	14.3.1.2.2.1	Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term by Age Group (Cohort A – North America, Europe, Australia)– Safety Population	
Table	14.3.1.2.2.2	Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term by Age Group (Cohort B – Japan) – Safety Population	
Table	14.3.1.2.3.1	Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term by Sex (Cohort A – North America, Europe, Australia)– Safety Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.3.1.2.3.2	Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term by Sex (Cohort B – Japan)– Safety Population	
Table	14.3.1.2.4.1	Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term by Usage of Most Commonly Used Anti-Epileptic Medications (Cohort A – North America, Europe, Australia)– Safety Population	
Table	14.3.1.2.4.2	Treatment-Emergent Adverse Events in Part 1 by MedDRA System Organ Class and Preferred Term by Usage of Most Commonly Used Anti-Epileptic Medications (Cohort B – Japan)– Safety Population	
Table	14.3.1.3.1.1	TEAEs Leading to Study Discontinuation in Part 1 by MedDRA System Organ Class and Preferred Term (Cohort A – North America, Europe, Australia)– Safety Population	
Table	14.3.1.3.1.2	TEAEs Leading to Study Discontinuation in Part 1 by MedDRA System Organ Class and Preferred Term (Cohort B – Japan) – Safety Population	
Table	14.3.1.4.1.1	Serious TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.3.1.4.1.2	Serious TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term (Cohort B – Japan) – Safety Population	
Table	14.3.1.5.1.1	Treatment Related TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term (Cohort A – North America, Europe, Australia)– Safety Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.3.1.5.1.2	Treatment Related TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term (Cohort B – Japan)– Safety Population	
Table	14.3.1.5.2.1	Treatment Related TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term by Age Group (Cohort A – North America, Europe, Australia)– Safety Population	
Table	14.3.1.5.2.2	Treatment Related TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term by Age Group (Cohort B – Japan)– Safety Population	
Table	14.3.1.5.3.1	Treatment Related TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term by Sex (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.3.1.5.3.2	Treatment Related TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term by Sex (Cohort B – Japan) – Safety Population	
Table	14.3.1.5.4.1	Treatment Related TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term by Usage of Most Common Concomitant Antiepileptic Medications (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.3.1.5.4.2	Treatment Related TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term by Usage of Most Common Concomitant Antiepileptic Medications (Cohort B – Japan) – Safety Population	
Table	14.3.1.6.1.1	TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term, and Maximum Severity (Cohort A – North America, Europe, Australia)– Safety Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Table	14.3.1.6.1.2	TEAEs in Part 1 by MedDRA System Organ Class and Preferred Term, and Maximum Severity (Cohort B – Japan)– Safety Population	
Table	14.3.1.7.1.1	Treatment-Emergent Adverse Events in Part 1 occurring in ≥ 5% of subjects by MedDRA System Organ Class and Preferred Term (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.3.1.7.1.2	Treatment-Emergent Adverse Events in Part 1 occurring in ≥ 5% of subjects by MedDRA System Organ Class and Preferred Term (Cohort B – Japan) – Safety Population	
Table	14.3.1.8.1.1	Overview of Treatment-Emergent Adverse Events of Special Interest during Part 1 (Cohort A – North America, Europe, Australia)– Safety Population	
Table	14.3.1.8.1.2	Overview of Treatment-Emergent Adverse Events of Special Interest during Part 1 (Cohort B – Japan) – Safety Population	
Table	14.3.1.9.1.1	Treatment-Emergent Adverse Events of Special Interest (AESI) by SOC and PT (Cohort A – North America, Europe, Australia) – Safety Population	
Table	14.3.1.9.1.2	Treatment-Emergent Adverse Events of Special Interest (AESI) by SOC and PT (Cohort B – Japan) – Safety Population	
Table	14.3.1.10.1.1.9	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects During the Part 1 Titration + Maintenance Period by System Organ Class and Preferred Term with Number of Events and Number of Resolved	New Post-hoc AE Table request. Table number adjusted to align with Part 2 SAP.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		Events (Cohort A – North America, Europe, Australia) - Safety Population	
Table	14.3.1.10.1.1.10	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects During the Part 1 Titration + Maintenance Period by System Organ Class and Preferred Term with Mean Onset and Mean Duration (Cohort A – North America, Europe, Australia) - Safety Population	New Post-hoc AE Table request. Table number adjusted to align with Part 2 SAP.
Table	14.3.1.10.1.1.11	Treatment-Emergent Adverse Events During the Part 1 Titration + Maintenance Period that Occurred in at Least 2% of Subjects in Either ZX008 Treatment Group and With Higher Percentage Than the Placebo Group by System Organ Class and Preferred Term (Cohort A – North America, Europe, Australia) - Safety Population	New Post-hoc AE Table request. Table number adjusted to align with Part 2 SAP.
Table	14.3.1.10.1.2.9	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects During the Part 1 Titration + Maintenance Period by System Organ Class and Preferred Term with Number of Events and Number of Resolved Events (Cohort B – Japan) -Safety Population	New Post-hoc AE Table request. Table number adjusted to align with Part 2 SAP.
Table	14.3.1.10.1.2.10	Treatment-Emergent Adverse Events that Occurred in at Least 5% of Subjects During the Part 1 Titration + Maintenance Period by System Organ Class and Preferred Term with Mean Onset and Mean Duration (Cohort B – Japan) - Safety Population	New Post-hoc AE Table request. Table number adjusted to align with Part 2 SAP.
Table	14.3.1.10.1.2.11	Treatment-Emergent Adverse Events During the Part 1 Titration + Maintenance Period that Occurred in at Least 2% of Subjects in Either ZX008 Treatment Group and With Higher Percentage Than the Placebo Group by System	New Post-hoc AE Table request. Table number adjusted to align with Part 2 SAP.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		Organ Class and Preferred Term (Cohort B – Japan) - Safety Population	
	14.3.2	**Listings of Deaths, Other Serious and Significant Adverse Events**	
Table	14.3.2.1	Listing of Deaths (Cohort A – North America, Europe, Australia)	
Table	14.3.2.2.1	Listing of SAEs (Cohort A – North America, Europe, Australia)	
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Output	16.1.9.2.1.2.1.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.2.1.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.2.1.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.1.2.1.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort A – North America, Europe, Australia)- MITT Population	
Output	16.1.9.2.1.2.1.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort A – North America, Europe, Australia)- MITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.1.2.1.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort B – Japan)- MITT Population	
Output	16.1.9.2.1.2.2.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.1.2.2.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.1.2.2.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	
Output	16.1.9.2.1.3.1.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.3.1.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.3.1.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.1.3.1.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.3.1.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.3.1.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis with Categorized Baseline Seizure Frequency and Baseline Seizure Frequency by Treatment Interaction (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.1.3.2.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.1.3.2.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.1.3.2.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.1.4.1.1	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.4.1.1s	Sensitivity Analysis of Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.4.1.1b	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	
Output	16.1.9.2.1.4.1.1c	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	
Output	16.1.9.2.1.4.1.2	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.1.4.2.1	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.1.4.2.1s	Sensitivity Analysis of Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.1.4.2.2	Percent Improvement in Frequency of Seizures resulting in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort B – Japan) – PP Population	
Output	16.1.9.2.1.6.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Age Subgroup: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Age Subgroup: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Sex: Nonparametric Analysis – (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.2s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Sex: Nonparametric Analysis – (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Weight Subgroup: Nonparametric Analysis – (Cohort A – North America, Europe, Australia) - mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.1.6.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Weight Subgroup: Nonparametric Analysis – (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Number of Concomitant Antiepileptic Medications Used: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.4s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Number of Concomitant Antiepileptic Medications Used: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.5	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Number of Prior Antiepileptic Medications Used: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.5s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Number of Prior Antiepileptic Medications Used: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.6	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Baseline Frequency of Seizures that Result in Drops: Nonparametric Analysis	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		(Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.6s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Baseline Frequency of Seizures that Result in Drops: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.7	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Race Group: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.1.6.8	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1 by Geographic Region: Nonparametric Analysis (Cohort A – North America, Europe, Australia) mITT Population	
Output	16.1.9.2.1.7.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 1 (Worst Value Substituted for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.7.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 1 (Worst Value Substituted for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.7.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis –	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		Sensitivity to Missing Data Analysis 1 (Worst Value Substituted for Dropouts) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	
Output	16.1.9.2.1.7.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 1 (Worst Value Substituted for Dropouts) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	
Output	16.1.9.2.1.7.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 1 (Worst Value Substituted for Dropouts) (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.1.7.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 2 (Differential Imputation Method for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.7.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 2 (Differential Imputation Method for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.1.7.3b	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 2 (Differential Imputation Method for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	
Output	16.1.9.2.1.7.3c	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 2 (Differential Imputation Method for Dropouts) (Cohort A – North America, Europe, Australia) – mITT Population (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	
Output	16.1.9.2.1.7.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Missing Data Analysis 2 (Differential Imputation Method for Dropouts) (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.1.9.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.9.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort A – North America, Europe, Australia) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.1.9.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	
Output	16.1.9.2.1.9.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	
Output	16.1.9.2.1.9.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Outliers (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.1.10.1	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.10.1s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.10.1b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.1.10.1c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	
Output	16.1.9.2.1.10.2	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis – Sensitivity to Seizure Clusters (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.1.10.3	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.10.3s	Sensitivity Analysis of Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.1.10.3b	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	
Output	16.1.9.2.1.10.3c	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort A – North America,	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	
Output	16.1.9.2.1.10.4	Frequency of Seizures Resulting in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cluster Event Sensitivity Analysis) (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.3.2.1.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.3.2.1.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.3.2.2.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.3.2.2.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	
Output	16.1.9.2.3.3.1.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia)– mITT Population	
Output	16.1.9.2.3.3.1.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.3.3.2.1	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.3.3.2.2	Frequency of Countable Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	
Output	16.1.9.2.3.4.1.1	Percent Improvement in Frequency of Countable Motor Seizures per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	
Output	16.1.9.2.3.4.1.2	Percent Improvement in Frequency of Countable Motor Seizures per 28 days during Part 1: Logistic Regression (Cohort B – Japan) – mITT Population	
	14.2.4.1	**Efficacy – Typical Drop Seizures**	
Output	16.1.9.2.4.1.2.1.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.4.1.2.1.1c	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – mITT Population	
Output	16.1.9.2.4.1.2.1.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.4.1.2.2.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.4.1.2.2.1b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – PP Population	
Output	16.1.9.2.4.1.2.2.1c	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3) – PP Population	
Output	16.1.9.2.4.1.2.2.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	
Output	16.1.9.2.4.1.3.1.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.4.1.3.1.1a	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.4.1.3.1.1b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.4.1.3.1.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.4.1.3.2.1	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.4.1.3.2.1b	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2) – PP Population	
Output	16.1.9.2.4.1.3.2.2	Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	
Output	16.1.9.2.4.1.4.1.1	Percent Improvement in Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	
Output	16.1.9.2.4.1.4.1.1b	Percent Improvement in Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population (Pre-DCR Seizure Event Dataset Version 2)	
Output	16.1.9.2.4.1.4.1.1c	Percent Improvement in Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population (Pre-DCR Seizure Event Dataset Version 3)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.4.1.4.1.2	Percent Improvement in Frequency of Seizures that Typically Result in Drops per 28 days during Part 1: Logistic Regression (Cohort B – Japan)– mITT Population	
	14.2.4.2	**Efficacy – Countable Non-Motor Seizures**	
Output	16.1.9.2.4.2.2.1.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.4.2.2.1.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.4.2.2.2.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.4.2.2.2.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	
Output	16.1.9.2.4.2.3.1.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.4.2.3.1.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.4.2.3.2.1	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.4.2.3.2.2	Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	
Output	16.1.9.2.4.2.4.1.1	Percent Improvement in Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	
Output	16.1.9.2.4.2.4.1.2	Percent Improvement in Frequency of Countable Non-Motor Seizures per 28 days during Part 1: Logistic Regression (Cohort B – Japan)– mITT Population	
	14.2.4.3	**Efficacy – All Countable Seizures (Motor + Non-Motor)**	
Output	16.1.9.2.4.3.2.1.1	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.4.3.2.1.2	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.4.3.2.2.1	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.4.3.2.2.2	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) – PP Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.4.3.3.1.1	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	
Output	16.1.9.2.4.3.3.1.2	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – mITT Population	
Output	16.1.9.2.4.3.3.2.1	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) – PP Population	
Output	16.1.9.2.4.3.3.2.2	Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) – PP Population	
Output	16.1.9.2.4.3.4.1.1	Percent Improvement in Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	
Output	16.1.9.2.4.3.4.1.2	Percent Improvement in Frequency of All Countable Seizures (Motor and Non-Motor) per 28 days during Part 1: Logistic Regression (Cohort B – Japan)– mITT Population	
	14.2.4.5	**All Countable Seizures that Did Not Result in Drops (ESC Confirmed)**	
Output	16.1.9.2.4.5.2.1.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1:	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
		Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.4.5.2.1.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) - mITT Population	
Output	16.1.9.2.4.5.2.2.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - PP Population	
Output	16.1.9.2.4.5.2.2.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Nonparametric Analysis (Cohort B – Japan) - PP Population	
Output	16.1.9.2.4.5.3.1.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.4.5.3.1.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) - mITT Population	
Output	16.1.9.2.4.5.3.2.1	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort A – North America, Europe, Australia) - PP Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.4.5.3.2.2	Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Parametric Analysis (Cohort B – Japan) - PP Population	
Output	16.1.9.2.4.5.4.1.1	Percent Improvement in Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.4.5.4.1.2	Percent Improvement in Frequency of All Countable Seizures that did not Result in Drops (ESC Confirmed) per 28 days during Part 1: Logistic Regression (Cohort B – Japan) - mITT Population	
Output	16.1.9.2.4.7.2.1.1	Frequency of Seizures Resulting in Drops (Caregiver Determination) per 28 days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) – mITT Population	New Post-hoc defined endpoint
Output	16.1.9.2.4.7.4.1.1	Percent Improvement in Frequency of Seizures Resulting in Drops (Caregiver Determination) per 28 days during Part 1: Logistic Regression (Cohort A – North America, Europe, Australia)– mITT Population	New Post-hoc defined endpoint
	14.2.5	**Efficacy – Seizure-free Days**	
Output	16.1.9.2.5.1.1	Number of seizure free days during Part 1: Nonparametric Analysis (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.5.1.2	Number of seizure free days during Part 1: Nonparametric Analysis (Cohort B – Japan) - mITT Population	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Output	16.1.9.2.5.2.1	Number of Drop Seizure Free Days per 28 Days (ESC Confirmed) during Part 1: Nonparametric Analysis: (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.5.2.1s	Sensitivity Analysis of Number of Drop Seizure Free Days per 28 Days (ESC Confirmed) during Part 1: Nonparametric Analysis: (Cohort A – North America, Europe, Australia) - mITT Population	
Output	16.1.9.2.5.2.2	Number of Drop Seizure Free Days per 28 Days (ESC Confirmed) during Part 1: Nonparametric Analysis (Cohort B – Japan) - mITT Population	
	16.2	**Subject data listing**	
	16.2.1	**Subject disposition and discontinuation**	
Listing	16.2.1.1.1	Subject Completion/Discontinuation in Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.1.1.2	Subject Completion/Discontinuation in Part 1 (Cohort B - Japan)	
	16.2.2	**Protocol deviations**	
Listing	16.2.2.1.1	Major Protocol Deviations in Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.2.1.2	Major Protocol Deviations in Part 1 (Cohort B - Japan)	
	16.2.3	**Subjects excluded from analysis**	
Listing	16.2.3.1.1	Subjects Excluded from the Per Protocol Population (Cohort A - North America, Europe, Australia)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.3.1.2	Subjects Excluded from the Per Protocol Population (Cohort B - Japan)	
Listing	16.2.3.2.1	Subject Allocation to Trial Populations (Cohort A - North America, Europe, Australia)	
Listing	16.2.3.2.2	Subject Allocation to Trial Populations (Cohort B - Japan)	
	16.2.4	**Demographic data and other baseline characteristics**	
Listing	16.2.4.1.1.1	Demographic data (Cohort A - North America, Europe, Australia)	
Listing	16.2.4.1.1.2	Demographic data (Cohort B - Japan)	
Listing	16.2.4.1.2.1	Informed Consent / Informed Assent in Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.4.1.2.2	Informed Consent / Informed Assent in Part 1 (Cohort B - Japan)	
Listing	16.2.4.1.4.1	% Change from Baseline in Weight and BMI (Cohort A - North America, Europe, Australia)	
Listing	16.2.4.1.4.2	% Change from Baseline in Weight and BMI (Cohort B - Japan)	
Listing	16.2.4.2.1.1	Medical History and Neurologic History (Cohort A - North America, Europe, Australia)	
Listing	16.2.4.2.1.2	Medical History and Neurologic History (Cohort B - Japan)	
Listing	16.2.4.2.3.1	Seizure history (Cohort A - North America, Europe, Australia)	
Listing	16.2.4.2.3.2	Seizure history (Cohort B - Japan)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.4.3.1.1	Medications and Therapies/Treatments Stopped during or up to 30 days prior to Screening (Cohort A - North America, Europe, Australia)	
Listing	16.2.4.3.1.2	Medications and Therapies/Treatments Stopped during or up to 30 days prior to Screening (Cohort B - Japan)	
Listing	16.2.4.3.2.1	Concomitant Medications and Therapies/Treatments (Cohort A - North America, Europe, Australia)	
Listing	16.2.4.3.2.2	Concomitant Medications and Therapies/Treatments (Cohort B - Japan)	
Listing	16.2.4.4.1.1	Prior Antiepileptic Drugs (AEDs)(Cohort A - North America, Europe, Australia)	
Listing	16.2.4.4.1.2	Prior Antiepileptic Drugs (AEDs)(Cohort B - Japan)	
Listing	16.2.4.4.2.1	Concomitant Antiepileptic Drugs (AEDs) (Cohort A - North America, Europe, Australia)	
Listing	16.2.4.4.2.2	Concomitant Antiepileptic Drugs (AEDs) (Cohort B - Japan)	
Listing	16.2.4.5.1.1	Rescue Medications (Cohort A - North America, Europe, Australia)	
Listing	16.2.4.5.1.2	Rescue Medications (Cohort B - Japan)	
	16.2.5	**Treatment exposure and compliance**	
Listing	16.2.5.1.1	IMP Intake per Day during Treatment (Cohort A - North America, Europe, Australia)	
Listing	16.2.5.1.2	IMP Intake per Day during Treatment (Cohort B - Japan)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.5.2.1	IMP Intake – Self Reported % Compliance (Cohort A - North America, Europe, Australia)	
Listing	16.2.5.2.2	IMP Intake – Self Reported % Compliance (Cohort B - Japan)	
Listing	16.2.5.3.1	Drug Accountability (Cohort A - North America, Europe, Australia)	
Listing	16.2.5.3.2	Drug Accountability (Cohort B - Japan)	
Listing	16.2.5.4.1	Background Antiepileptic Drugs (AEDs) Pharmacokinetic Concentrations (Cohort A - North America, Europe, Australia)	
Listing	16.2.5.4.2	Background Antiepileptic Drugs (AEDs) Pharmacokinetic Concentrations (Cohort B - Japan)	
	16.2.6	**Efficacy data**	
Listing	16.2.6.1.1.1	Recorded Seizures – Duration and Number of Occurrences per Subject (Diary data) (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.1.1.2	Recorded Seizures – Duration and Number of Occurrences per Subject (Diary data) (Cohort B - Japan)	
Listing	16.2.6.1.2.1	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline during Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.1.2.1s	Sensitivity Analysis of Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline during Part 1 (Cohort A - North America, Europe, Australia)	New Listing using Supplemental Seizure File updated post-Part 1 Database Lock

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.6.1.2.1c	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline during Part 1 (Cluster Sensitivity) (Cohort A - North America, Europe, Australia)	New Listing due to request for Cluster Sensitivity
Listing	16.2.6.1.2.1cs	Sensitivity Analysis of Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline during Part 1 (Cluster Sensitivity) (Cohort A - North America, Europe, Australia)	New Listing using Supplemental Seizure File updated post-Part 1 Database Lock
Listing	16.2.6.1.2.1b	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline during Part 1 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 2)	New Listing using Pre-DCR dataset Version 2
Listing	16.2.6.1.2.1c3	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline during Part 1 (Cohort A - North America, Europe, Australia) (Pre-DCR Seizure Event Dataset Version 3)	New Listing using Pre-DCR dataset Version 3
Listing	16.2.6.1.2.2	Change in Seizure Frequency Resulting in Drops (ESC Confirmed) from Baseline during Part 1 (Cohort B - Japan)	
Listing	16.2.6.2.1	Clinical Global Impression – Improvement Rating as Assessed by the Investigator and Subject or Parent/Caregiver (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.2.2	Clinical Global Impression – Improvement Rating as Assessed by the Investigator and Subject or Parent/Caregiver (Cohort B - Japan)	
Listing	16.2.6.3.1	Change in Countable Motor Seizures from Baseline during Part 1 (Cohort A - North America, Europe, Australia)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.6.3.2	Change in Countable Motor Seizures from Baseline during Part 1 (Cohort B - Japan)	
Listing	16.2.6.4.1	Duration of Longest Interval between Seizures during Titration and Maintenance Resulting in Drops (ESC Confirmed) in Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.4.1s	Sensitivity Analysis of Duration of Longest Interval between Seizures during Titration and Maintenance Resulting in Drops (ESC Confirmed) in Part 1 (Cohort A - North America, Europe, Australia)	New Listing using Supplemental Seizure File updated post-Part 1 Database Lock
Listing	16.2.6.4.2	Duration of Longest Interval between Seizures during Titration and Maintenance Resulting in Drops (ESC Confirmed) in Part 1 (Cohort B – Japan)	
Listing	16.2.6.5.1	Change in Seizures that Typically Result in Drops from Baseline during Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.5.1b	Change in Seizures that Typically Result in Drops from Baseline during Part 1 (Cohort A - North America, Europe, Australia) (Pre-DCR Version 2)	
Listing	16.2.6.5.1c	Change in Seizures that Typically Result in Drops from Baseline during Part 1 (Cohort A - North America, Europe, Australia) (Pre-DCR Version 3)	
Listing	16.2.6.5.2	Change in Seizures that Typically Result in Drops from Baseline during Part 1 (Cohort B - Japan)	
Listing	16.2.6.6.1	Change in Countable Non-Motor Seizures from Baseline during Part 1 (Cohort A - North America, Europe, Australia)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.6.6.2	Change in Countable Non-Motor Seizures from Baseline during Part 1 (Cohort B - Japan)	
Listing	16.2.6.7.1	Change in All Countable Seizures (Motor + Non-Motor) from Baseline during Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.7.2	Change in All Countable Seizures (Motor + Non-Motor) from Baseline during Part 1 (Cohort B - Japan)	
Listing	16.2.6.13.1	Change in Rescue Medication Usage from Baseline during Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.13.2	Change in Rescue Medication Usage from Baseline during Part 1 (Cohort B - Japan)	
Listing	16.2.6.14.1	Seizure Free Days during Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.14.2	Seizure Free Days during Part 1 (Cohort B - Japan)	
Listing	16.2.6.14.3	Drop Seizure Free Days (ESC Confirmed) during Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.14.3s	Sensitivity Analysis of Drop Seizure Free Days (ESC Confirmed) during Part 1 (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.14.4	Drop Seizure Free Days (ESC Confirmed) during Part 1 (Cohort B - Japan)	
Listing	16.2.6.15.1	Hospitalizations and Medical Services (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.15.2	Hospitalizations and Medical Services (Cohort B - Japan)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.6.17.1	Quality of Life in Childhood Epilepsy (QOLCE) Scale (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.17.2	Quality of Life in Childhood Epilepsy (QOLCE) Scale (Cohort B - Japan)	
Listing	16.2.6.18.1	Zarit Caregiver Burden Inventory (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.18.2	Zarit Caregiver Burden Inventory (Cohort B - Japan)	
Listing	16.2.6.19.1	Parent/Caregiver Ratings using HADS Scale (Cohort A - North America, Europe, Australia)	
Listing	16.2.6.19.2	Parent/Caregiver Ratings using HADS Scale (Cohort B - Japan)	
Listing	16.2.6.20.1	Change in All Countable Seizures that did not Result in Drops (ESC Confirmed) from Baseline during Part 1 (Cohort A - North America, Europe, Australia)	New post-hoc defined endpoint
Listing	16.2.6.20.2	Change in All Countable Seizures that did not Result in Drops (ESC Confirmed) from Baseline during Part 1 (Cohort B - Japan)	New post-hoc defined endpoint
Listing	16.2.6.21.1	Change in Seizure Frequency Resulting in Drops (Caregiver Determination) from Baseline during Part 1 (Cohort A - North America, Europe, Australia)	New post-hoc defined endpoint
Listing	16.2.6.21.2	Change in Seizure Frequency Resulting in Drops (Caregiver Determination) from Baseline during Part 1 (Cohort B - Japan)	New post-hoc defined endpoint
	16.2.7	**Adverse events**	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.7.1.1	Adverse Events (Cohort A - North America, Europe, Australia)	
Listing	16.2.7.1.2	Adverse Events (Cohort B - Japan)	
Listing	16.2.7.2.1	Adverse Events of Special Interest (AESI) (Cohort A - North America, Europe, Australia)	
Listing	16.2.7.2.2	Adverse Events of Special Interest (AESI) (Cohort B - Japan)	
	16.2.8	**Laboratory data**	
Listing	16.2.8.1.1.1	Laboratory Data Hematology Parameters (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.1.1.2	Laboratory Data Hematology Parameters (Cohort B - Japan)	
Listing	16.2.8.1.2.1	Extreme Value Laboratory Parameters – Hematology (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.1.2.2	Extreme Value Laboratory Parameters – Hematology (Cohort B - Japan)	
Listing	16.2.8.2.1.1	Laboratory Data Biochemistry Parameters (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.2.1.2	Laboratory Data Biochemistry Parameters (Cohort B - Japan)	
Listing	16.2.8.2.2.1	Extreme Value Laboratory Parameters – Biochemistry (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.2.2.2	Extreme Value Laboratory Parameters – Biochemistry (Cohort B - Japan)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.8.3.1.1	Laboratory Data Coagulation Parameters (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.3.1.2	Laboratory Data Coagulation Parameters (Cohort B - Japan)	
Listing	16.2.8.4.1.1	Laboratory Data Urinalysis Parameters (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.4.1.2	Laboratory Data Urinalysis Parameters (Cohort B - Japan)	
Listing	16.2.8.4.2.1	Extreme Value Urinalysis Data (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.4.2.2	Extreme Value Urinalysis Data (Cohort B - Japan)	
Listing	16.2.8.5.1	Tests of Growth, Precocious Puberty and Thyroid Function (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.5.2	Tests of Growth, Precocious Puberty and Thyroid Function (Cohort B - Japan)	
Listing	16.2.8.6.1	Urine and Serum Pregnancy tests (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.6.2	Urine and Serum Pregnancy tests (Cohort B - Japan)	
Listing	16.2.8.7.1	Urine and Serum THC panel (Cohort A - North America, Europe, Australia)	
Listing	16.2.8.7.2	Urine and Serum THC panel (Cohort B - Japan)	
Listing	16.2.8.8.1	Laboratory Data: Listing of Test Comments from Lab Vendor for All Laboratory Parameters (Cohort A - North America, Europe, Australia)	New Listing added.

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.8.8.2	Laboratory Data: Listing of Test Comments from Lab Vendor for All Laboratory Parameters (Cohort B – Japan)	New Listing added.
	16.2.9	**Other Safety Data**	
Listing	16.2.9.1.1.1	Vital Signs (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.1.1.2	Vital Signs (Cohort B - Japan)	
Listing	16.2.9.1.2.1	Abnormal Vital Signs Data (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.1.2.2	Abnormal Vital Signs Data (Cohort B - Japan)	
Listing	16.2.9.2.1	Columbia-Suicide Severity Rating Scale (C-SSRS) (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.2.2	Columbia-Suicide Severity Rating Scale (C-SSRS) (Cohort B - Japan)	
Listing	16.2.9.3.1.1	Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) – Individual Questions (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.3.1.2	Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) – Individual Questions (Cohort B - Japan)	
Listing	16.2.9.3.2.1	Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) – Summary Scales and Indexes (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.3.2.2	Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) – Summary Scales and Indexes (Cohort B - Japan)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.9.3.3.1	Behavior Rating Inventory of Executive Function (BRIEF) – Individual Questions (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.3.3.2	Behavior Rating Inventory of Executive Function (BRIEF) – Individual Questions (Cohort B - Japan)	
Listing	16.2.9.3.4.1	Behavior Rating Inventory of Executive Function (BRIEF) – Summary Scales and Indexes (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.3.4.2	Behavior Rating Inventory of Executive Function (BRIEF) – Summary Scales and Indexes (Cohort B - Japan)	
Listing	16.2.9.3.5.1	Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) – Individual Questions (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.3.5.2	Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) – Individual Questions (Cohort B - Japan)	
Listing	16.2.9.3.6.1	Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) – Summary Scales and Indexes (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.3.6.2	Behavior Rating Inventory of Executive Function Adult Version (BRIEF-A) – Summary Scales and Indexes (Cohort B - Japan)	
Listing	16.2.9.4.1	Tanner Staging (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.4.2	Tanner Staging (Cohort B - Japan)	

Table/ Figure/ Listing	Number	Table Header	Description of Modification(s)
Listing	16.2.9.5.1	Physical Examination and Neurologic Examination (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.5.2	Physical Examination and Neurologic Examination (Cohort B - Japan)	
Listing	16.2.9.7.1	Epilepsy Genotype panel (Cohort A - North America, Europe, Australia)	
Listing	16.2.9.7.2	Epilepsy Genotype panel (Cohort B - Japan)	