CLINICAL STUDY PROTOCOL

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
Study Number:	ZX008-1601
Study Product:	Fenfluramine Hydrochloride Oral Solution; ZX008
IND Number:	132604
EudraCT Number:	2017-002628-26
Sponsor:	Zogenix International Limited A wholly owned subsidiary of Zogenix, Inc. 5959 Horton Street, Suite 500 Emeryville, CA 94608 USA
Sponsor's Medical Contact:	Bradley S. Galer, MD Chief Medical Officer Zogenix, Inc.
Date and Version of Study Protocol:	08 June 2020 (Amendment 3.0) 29 July 2019 (Amendment 2.1) 10 January 2018 (Amendment 1.0 ROW) 13 July 2017 Version 1.1 (Original Protocol)

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator Study File. This list will be updated by the Sponsor or the Sponsor's agent and provided to study sites as needed.

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SIGNATURE OF SPONSOR

Study Number:	ZX008-1601 Protocol Amendment 3.0 08 June 2020
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Sponsor's Responsible Officer:	Gail M. Farfel, PhD Zogenix International Limited A wholly owned subsidiary of Zogenix, Inc. 5959 Horton Street, FL 5 Emeryville, CA 94608 USA

	9 June 2020
Signature	**Date (Day/Month/Year)**

SIGNATURE(S) OF THE PRINCIPAL INVESTIGATOR

Study Number:	ZX008-1601 Protocol Amendment 3.0 08-June-2020
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

I have read this study protocol, including all appendices. By signing this study protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

Name and affiliation to be filled out by the investigator

Principal Investigator
(Name & Affiliation):

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

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AS	atonic seizure
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve from time zero to time=t
BID	bis in die; two times per day
BMI	body mass index
BRIEF	Behavior Rating Inventory of Executive Function
C-SSRS	Columbia-Suicide Severity Rating Scale
$C_{avg•ss}$	average plasma concentration
CBD	cannabidiol
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
C_{max}	maximum observed concentration determined directly from the concentration-time profile
CRF	case report form
CS	clonic seizures
CYP	cytochrome p450
dL	deciliter
DS	Dravet syndrome
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EEG	electroencephalogram
EOS	End of Study
EPAR	European Public Assessment Report
ET	early termination
FS	focal seizure
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GH	growth hormone
GMP	Good Manufacturing Practices
GTC	generalized tonic-clonic seizure
HADS	Hospital Anxiety and Depression Scale
HIV	human immunodeficiency virus
HR	heart rate
IB	Investigators' Brochure
ICF	informed consent form
ICH	International Council on Harmonization
IDSMC	Independent Data and Safety Monitoring Committee
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IHC	immunohistochemistry
ILAE	International League Against Epilepsy
IMP	investigational medicinal product
IND	Investigational New Drug

Abbreviation	Definition
ICAB	International Cardiology Advisory Board
IRB	Institutional Review Board
IU	international unit
IWR	interactive web response (system)
KD	ketogenic diet
kg	kilogram
Leiter-3	Leiter International Performance Scale-Revised
LGS	Lennox-Gastaut syndrome
LH	luteinizing hormone
M	Maintenance period
MCDS	mean change in number of seizures that results in drops
MCSF	mean convulsive seizure frequency
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg/day	milligram per kilogram per day
min	minutes
mITT	modified intent-to-treat
mL	milliliter
MS	myoclonic seizure
OLE	open-label extension
PopPK model	population pharmacokinetic model
PK	pharmacokinetics
PP	per protocol
QoL	Quality of Life
QOLCE	Quality of Life in Childhood Epilepsy
QTcF	corrected QT interval using Fredericia method
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SE	status epilepticus
SMEI	severe myoclonic epilepsy of infancy
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy
T+M	Titration plus Maintenance periods
$t_{1/2}$	terminal half-life
TA	tonic/atonic seizure
THC	tetrahydrocannabinol
T_{max}	time to maximum concentration
TS	tonic seizure
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
USP	United States Pharmacopeia
VABS	Vineland Adaptive Behavior Scale
VNS	vagal nerve stimulator/stimulation
ZX008	fenfluramine hydrochloride oral solution

STUDY SYNOPSIS

<table>
<tr><td colspan="2">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</td></tr>
<tr><td colspan="2">Study Number: ZX008-1601</td></tr>
<tr><td colspan="2">Study Product: Fenfluramine Hydrochloride Oral Solution, ZX008</td></tr>
<tr><td>Type of Study:
Part 1: Efficacy and safety study
Part 2: Long-term safety study</td><td>Indication Studied:
Adjunctive therapy for seizures in Lennox-Gastaut syndrome (LGS)</td></tr>
<tr><td>Phase of Development: Phase III</td><td>Countries: North America, Europe, Japan, and Australia</td></tr>
<tr><td colspan="2">Sponsor: Zogenix International Limited</td></tr>
<tr><td colspan="2">Coordinating Investigator: Kelly Knupp, M.D.</td></tr>
<tr><td colspan="2">Estimated Duration of Individual Subject Participation:
The duration of participation in the study for an individual subject in the double-blind study (Part 1) is expected to be up to 20 weeks. The duration of participation in the open-label extension (Part 2) is up to 54 weeks for a total participation time of up to 74 weeks. Regardless of whether subjects end participation early, do not continue with the open-label extension, or roll over to the open-label extension, all subjects will have follow-up visits after the last dose of study medication for final safety monitoring. 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.</td></tr>
<tr><td colspan="2">Objectives:

The primary objective of Part 1 is the primary objective of the entire study.

<u>Part 1</u>
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 between baseline and the combined Titration and Maintenance Periods (T+M)
The key secondary objectives of Part 1 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 frequency of seizures that result in drops between baseline and 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 rating, as assessed by the Principal Investigator

See Statistical Methods (Section 10.1.6.1) for hierarchical testing procedure.</td></tr>
</table>

Additional secondary efficacy objectives of Part 1 are:

- To evaluate the effect of ZX008 0.2 and 0.8 mg/kg/day (independently) versus placebo on the following endpoints:
  - 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 [AS], tonic/atonic seizures [TA], clearly recognizable focal seizures [FS], and myoclonic seizures [MS] that result in a drop)
  - Change in the frequency of all countable seizures (i.e., motor and nonmotor) between baseline and T+M
  - Change in frequency of seizures that 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
  - The proportion of subjects who achieve a worsening or no change (i.e., ≤ 0% reduction), >0%, ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (i.e. 0 or 1 seizures) 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;; and in all seizures that result in drops
  - Number of seizure-free days, defined as 1) days with no countable seizures and 2) days with no seizures that result in drops
  - Longest interval between 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 rating, as assessed by the parent/caregiver

The safety objectives of Part 1 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 BMI
- To evaluate the change from baseline in cognition using age-appropriate Behavior Rating Inventory of Executive Function (BRIEF)

The pharmacokinetic (PK) objective of Part 1 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.

The exploratory objectives of Part 1 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 QoL using the Quality of Life in Childhood Epilepsy (QOLCE) Assessment
  - 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 used to treat seizures
  - The incidence of status epilepticus

Part 2

The primary objective of Part 2 is:

- To assess the long-term safety and tolerability of ZX008 in children and adults with LGS with regard to adverse events (AEs), laboratory parameters, physical examination, neurological examination, suicidality, cognition (BRIEF), vital signs (blood pressure, heart rate, temperature, and respiratory rate), electrocardiograms (ECG), echocardiograms (ECHO), body weight, and BMI.

The secondary objectives of Part 2 are:

- To assess the effect of ZX008 relative to the Part 1 baseline on the following effectiveness measures:
  - The change in the frequency of seizures that result in drops
  - The change in the frequency of all countable motor seizures (GTC, TS, CS, AS, TA, FS, MS with a drop)
  - The change in the frequency of all countable seizures
  - The proportion of subjects who achieve a worsening or no change (ie, ≤ 0% reduction), >0%, ≥25%, ≥50%, ≥75%, 100% reduction, and "near seizure freedom" (ie 0 or 1 seizures) in frequency of all countable seizures that result in drops, countable motor seizures that do not result in drops, all countable motor seizures, all countable seizures, and all countable seizures that do not result in drops
  - Number of seizure-free days, defined as 1) days with no countable seizures and 2) days with no seizures that result in drops
  - Longest interval between seizures that result in drops

- To evaluate the effect of ZX008 on the following endpoints:
  - Clinical Global Impression – Improvement rating, as assessed by the Principal Investigator
  - Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver

The exploratory objectives of Part 2 are:

- To determine the incidence of the following on subjects receiving ZX008:
  - The incidence of medical services used to treat seizures
  - The incidence of status epilepticus
  - The use of rescue medication

- To assess the effect of ZX008 on the following measures:
  - The change from baseline in 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)

Methodology:
This is an international multicenter study being conducted in two parts. Up to approximately 80 study sites in North America, Europe, Japan, and Australia are initially 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. The study will include 2 cohorts: Cohort A will include randomized subjects from North America, Europe, and Australia; Cohort B will include randomized subjects from Japan only. The primary study endpoint

is assessed from Part 1 Cohort A data. The primary analysis will be conducted when the last subject in Cohort A has completed Part 1. Cohort B will be analyzed independently with the analysis occurring after the last subject in Cohort B completes Part 2. Part 2 will be an open-label, flexible-dose extension for subjects completing Part 1 of the study.

Part 1 will consist of a 4-week baseline, 2-week titration, 12-week maintenance, and 2-week taper or transition period. The 4--week Baseline Period will consist 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 will be randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 mg/day [or 0.5 mg/kg/day, maximum 20 mg/day, for subjects taking concomitant STP]) or placebo. Randomization will be stratified by weight (<37.5 kilograms [kg], ≥37.5 kg) to ensure balance across treatment arms, and at least 25% of subjects will be in each weight group. All subjects will be titrated to their blinded randomized dose over a 2-week Titration Period. Following titration, subjects will continue treatment at their randomly assigned dose over a 12-week Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is 14 weeks. 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 will 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-ups will be 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. Follow-ups will include ECHO, ECG, and physical exam. Subjects in France and Netherlands will also have a chest x-ray.

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 will consist of a 12-month Open-Label Extension (OLE) Treatment Period and a 2-week Post-Dosing Period. Thus, subjects who complete Part 2 will have been treated with ZX008 for at least 70 weeks (including their participation in both Part 1 and Part 2). If ZX008 is not commercially available for the treatment of seizures associated with LGS after the end of the OLE Treatment Period, subjects may continue to receive ZX008 in a separate extension protocol. Continuation will be based on benefit/risk and will be offered to subjects who continue to meet eligibility requirements and comply with Investigator's instructions.

During Part 2 all subjects will be treated initially with 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study subjects and determine the minimally effective dose. 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 maximum 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/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.

Cardiac safety follow-ups will be performed after study drug discontinuation for early termination and for those subjects who complete Part 2. 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. Follow-ups will include ECHO, ECG, and physical exam. Subjects in France and Netherlands will also have a chest x-ray.

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. Seizures that result in a drop are defined as seizures involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the subject's head hitting a surface or that could have led to a fall or injury, depending on the patient's position at the time of the seizure.

A schedule of assessments for Part 1 is provided in Table 1 and for Part 2 in Table 2.

External Individuals and Committees: The ZX008 clinical program will employ an Independent Data and Safety Monitoring Committee (IDSMC) that will be responsible for safety oversight. A separate International Cardiology Advisory Board (ICAB) advises the Sponsor on matters of cardiac safety of the ZX008 clinical trials. ECGs and Doppler ECHOs will be centrally read and interpreted under blinded conditions using pre-specified criteria, and if necessary, with review by the ICAB.

Number of Subjects:
Approximately 340 subjects will be screened and approximately 250 subjects will be randomized into Part 1 Cohort A, and at least 30 and up to 50 subjects will be randomized into Part 1 Cohort B. The number of screened subjects may exceed 340 depending on the screen fail rate. Only subjects that participated in Part 1 are eligible for participation in Part 2. Each clinical site will not randomize more than a maximum of 15 subjects into Part 1 without prior consent from the Sponsor.

Selection Criteria for Part 1

Inclusion Criteria: All subjects must meet all of the following inclusion criteria to be enrolled into the study:

1. Subject is male or nonpregnant, nonlactating female, age 2 to 35 years, inclusive as of the day of the Screening Visit. Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative urine or serum pregnancy test at screening. Subjects of childbearing or child-fathering potential must be willing to use medically acceptable forms of birth control (see Section 4.4.2), which includes abstinence, while being treated on this study and for 90 days after the last dose of study drug.
2. Subject must have a diagnosis of Lennox-Gastaut syndrome, where seizures that result in drops are not completely controlled by current antiepileptic treatments. (Subjects without a formal diagnosis may still be enrolled after review and consultation between the Investigator and Sponsor, and in some cases, the Epilepsy Study Consortium. Final decisions on enrollment are at the discretion of the sponsor if all other criteria are met.)
3. Subjects must meet all of the following 4 criteria for Lennox-Gastaut syndrome, as defined in this protocol:
    a. Onset of seizures at 11 years of age or younger.
    b. Multiple seizure types (must include TS or TA), including countable motor seizures that result in drops. Countable motor seizure types eligible for inclusion are: GTC, TS, CS, AS, FS with observable motor symptoms, and MS with a drop.
    c. Abnormal cognitive development.
    d. Evidence of EEG in the medical history that shows abnormal background activity accompanied by slow spike and wave pattern <2.5 Hz. (Acceptable evidence includes a

copy of the EEG trace, EEG report, or physician note that appropriately describes the EEG findings.)

4. Subject must have had at least 8 drop seizures in the last 4 weeks prior to Screening (minimum of 4 drop seizures in the first two weeks and 4 in the last two weeks before Screening), by parent/guardian report to Investigator or investigator medical notes
5. Receiving at least 1 concomitant AED and up to 4 concomitant AEDs, inclusive. KD and VNS are permitted but do not count towards the total number of AEDs. Rescue medications for seizures are not counted towards the total number of AEDs.
6. All medications or interventions for epilepsy (including KD and VNS) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
7. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
8. Subject has provided assent in accordance with Institutional Review Board (IRB)/Ethics Committee requirements, if capable.
9. Subject's parent/caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.

Exclusion Criteria: Subjects who meet any of the following exclusion criteria will not be enrolled into the study:

1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication.
2. Subject's etiology of seizures is a degenerative neurological disease.
3. Subject has a history of hemiclonic seizures in the first year of life.
4. Subject only has drop seizures in clusters, where individual seizures cannot be counted reliably.
5. Subject has pulmonary arterial hypertension.
6. Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke, or clinically significant structural cardiac abnormality, including but not limited to mitral valve prolapse, atrial or ventricular septal defects, patent ductus arteriosus (note: Patent Foramen Ovale or a bicuspid valve are not considered exclusionary).
7. Subject has current or recent history of Anorexia Nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month.
8. Subject has a current or past history of glaucoma.
9. Subject has had an anoxic episode requiring resuscitation within 6 months of the Screening Visit.
10. Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x ULN and/or elevated bilirubin <2x ULN) may be entered into the study after review and approval by the Medical Monitor in conjunction with the Sponsor, in consideration of comorbidities and concomitant medications.
11. Subject has severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73m^2)
12. Subject is receiving concomitant therapy with any of the following: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; other centrally-acting noradrenergic agonists, including atomoxetine; or cyproheptadine (see Appendix 1 for a list of prohibited medications). (Note: Short-term medication requirements for prohibited medications will be handled on a per case basis by the Medical Monitor.)
13. Subject has positive result on urine or serum tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at the Screening Visit.

14. Subject is taking felbamate for less than 1 year prior to screening and/or does not have stable liver function and hematology laboratory tests, and/or the dose has not been stable for at least 60 days prior to the Screening Visit.
15. Subject is known to be human immunodeficiency virus (HIV) positive.
16. Subject is known to have active viral hepatitis (B or C)
17. Subject is currently receiving an investigational product.
18. Subject has participated in another clinical trial within the past 30 days (calculated from that study's last scheduled visit). Participation in nontreatment trials will be reviewed by the medical monitor.
19. Subject is at imminent risk of self-harm or harm to others, in the Investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must be excluded if they report suicidal behavior in the past 6 months as measured by the C-SSRS at Screening or Baseline, which includes suicidal ideation with intent and plan (Item #5). If a subject reports suicidal ideation on Item 4 without specific plan, and the Investigator feels that the subject is appropriate for the study considering the potential risks, the Investigator must document appropriateness for inclusion, and discuss with the parent/caregiver to be alert to mood or behavioral changes, especially around times of dose adjustment.
20. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
21. Subject is institutionalized in a general nursing home (ie, in a facility that does not provide skilled epilepsy care).
22. Subject does not have a reliable caregiver who can provide seizure diary information throughout the study.
23. Subject has a clinically significant condition, including chronic obstructive pulmonary disease, interstitial lung disease, or portal hypertension, or has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to the Screening Visit, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

Randomization Inclusion Criteria: Subjects must meet all of the inclusion criteria and none of the exclusion criteria above and meet the following criteria in order to be randomized:

1. Subject has been approved for study inclusion by the Epilepsy Study Consortium.
2. Subject does not have an exclusionary cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination and is approved for entry by the central cardiac reader. Exclusionary abnormalities include, but are not limited to:
    a. Trace or greater mitral or aortic valve regurgitation in subjects ≤18 years of age
    b. Mild or greater mitral or aortic valve regurgitation in subjects >18 years of age
    c. Possible signs of pulmonary hypertension with abnormal or greater than upper range of normal values
    d. Evidence of left ventricular dysfunction (systolic or diastolic)
3. Subject demonstrates a stable baseline with ≥ 2 seizures per week resulting in drops during the 4-week Baseline Period.
4. Subject's parent/caregiver has been compliant with diary completion during the Baseline Period, in the opinion of the Investigator and Sponsor.

Selection Criteria for Part 2

To be included in Part 2:

1. Subjects must continue to meet the Selection Criteria for Part 1 (except for criteria related to seizure frequency). If a subject entering Part 2 does not meet Randomization Criteria 2 regarding cardiovascular abnormalities, Section 8.9.1 Follow-up of Cardiovascular Findings will be applied to determine eligibility to continue into Part 2.

2. All subjects must have satisfactorily completed Part 1 of the study in the opinion of the Investigator and the Sponsor.
3. Review of inclusion and exclusion criteria and written informed parental or guardian consent and assent of minors (if the subject is capable of providing assent) for Part 2 must be obtained before a subject can start any of the Part 2 Visit 15 procedures.
4. Subjects must, in the medical opinion of the Investigator, be candidates for continued treatment for an extended period of time with ZX008. Candidates for continuous treatment should not meet Discontinuation criteria listed in Section 4.5 and should not meet the following criteria:
    a. Clinically meaningful worsening of seizures, judged by Investigator or subject/caregiver such that treatment outside of the protocol and other than ZX008 is assumed to be in the subject's best interest. A clinically meaningful worsening is an increase in frequency, severity or duration of existing seizures, or (in some cases) emergence of a new seizure type. Frequent or increased use of rescue medication may be considered indicative of worsening.
    b. Clinically significant clinical laboratory findings (eg, elevated ALT levels, decrease in platelet count, etc. that are CTCAE Grade 3 or higher) in subjects with no prior relevant history, that were not present during Baseline, are confirmed by a repeat test within a week, and not attributable to other concomitant medications.
    c. Weight loss >15% during the T+M period that has not stabilized and is considered, in the opinion of the Investigator, detrimental to continuing treatment with ZX008.
5. Those subjects who do not complete the 12-week Maintenance Period of Part 1 may, on a case-by-case basis, be eligible for entrance after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a ZX008 trial. The decision whether to permit participation in Part 2 for subjects who do not complete Part 1 resides solely with the Sponsor, who will require a formal request for early Part 2 continuation to be made by the site Investigator as well as an evaluation of risk/benefit. The Sponsor may also consult with the ICAB and/or the IDSMC, and take into consideration evidence of the following for approval:
    a. The subject is experiencing a worsening in condition that is not likely to be related to Part 1 treatment, in the opinion of the Investigator
    b. The subject has progressed at least half-way through Part 1 (ie, Visit 8)
    c. The subject has been compliant with assessments and requirements of Part 1
    d. The subject does not exhibit other contraindications to initiating open-label treatment

Study Product, Dose, and Mode of Administration:

ZX008 is supplied as an oral solution in concentrations of 1.25, 2.5, and 5 mg/mL. Subjects will be randomized to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 mg/day) or placebo. Study medication will be administered twice a day (BID) in equally divided doses. (Note that subjects taking concomitant stiripentol [STP] will be randomized to 0.5 mg/kg/day, maximum dose 20 mg/day, or equivalent volume of placebo. Subjects randomized to 0.5 mg/kg/day will be included in analyses with the subjects randomized to 0.8 mg/kg/day not taking STP.)

Reference Product, Dose, and Mode of Administration:

Matching ZX008 placebo is supplied as an oral solution.

Duration of Treatment:

In Part 1 all subjects will receive ZX008 or matching placebo for up to approximately 16 weeks (Titration Period=2 weeks; Maintenance Period=12 weeks; Taper/Transition Period=2 weeks). At the end of the 12-week Maintenance Period, eligible subjects may enroll into Part 2, the open-label extension, after completing a 2-week transition period with blinded study medication. Subjects who enroll in Part 2 will receive ZX008 for up to 54 weeks (which includes a 2-week taper at the end of the

open-label extension). Subjects who do not enroll in the open-label extension will undergo a taper off of study medication (doses will be administered in a blinded fashion similar to the titration, ie, doses will be decreased in 4-day increments). Follow-up cardiovascular safety assessments will be performed following the last dose of study medication for all subjects, regardless of whether they complete the entire study or terminate early, unless the subject was known to be taking placebo (ie, blind was broken). These follow-ups will occur 3 months following the last dose of study medication for any subject taking the medication for 2-13 weeks, and at least 3 and 6 months following the last dose for any subject taking the medication for >13 weeks. Additionally, 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.

Criteria for Evaluation:

Efficacy:

The efficacy endpoints for Part 1 of the study are:

Primary Endpoint:
Percent change from baseline in the frequency of seizures that result in drops in the combined Titration and Maintenance Periods (T+M) in the ZX008 0.8 mg/kg/day group compared to the placebo group.

Key Secondary Endpoints:

- Change from baseline in the frequency of seizures that result in drops 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 clinically-meaningful improvement (much or very much improved) in the Clinical Global Impression – Improvement as assessed by Principal Investigator comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.

Additional Secondary Endpoints:

- Change from baseline in the frequency of all countable motor seizures in T+M in the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo
    - Countable motor 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
- Change from baseline in the frequency of countable seizures that result in drops
- Change from baseline in the frequency of seizures that result in drops between baseline and the Maintenance Period (M)
- Change from baseline in frequency of countable seizures that do not result in drops
- 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
- 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
- The longest interval (days) between seizures that result in drops 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

The efficacy endpoints for Part 2 of the study are:

- The change from baseline in the frequency of seizures that result in drops.
- The change from baseline in the frequency of all countable motor seizures (GTC, TS, CS, AS, TA, FS, MS with a drop)
- The change from baseline in the frequency of all countable seizures
- The 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) from baseline in frequency of all countable seizures that result in drops, countable motor seizures that do not result in drops, all countable motor seizures, all countable seizures, and all countable seizures that do not result in drops
- Number of seizure-free days, defined as 1) days with no countable seizures and 2) days with no seizures that result in drops
- Clinical Global Impression – Improvement rating, as assessed by the Principal Investigator.
- Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver.

Safety:

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

- AEs
- Laboratory safety (hematology, chemistry, urinalysis)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- 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)
- Body weight and BMI

Exploratory:

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

- Incidence of status epilepticus
- Incidence of rescue medication usage
- Number of days rescue medication used
- Incidence in use of medical services to treat seizures
- The change from baseline in behavior using the Vineland Adaptive Behavior Scale (VABS) (Part 1 only)
- The change from baseline in quality of life using the QOLCE
- The change from baseline in caregiver burden using the Zarit Caregiver Burden Inventory
- The change from baseline in affective symptoms of parent/caregiver using the HADS scale

Pharmacokinetics:
Steady-state plasma fenfluramine and norfenfluramine PK parameters (maximum and minimum plasma concentration (, $C_{min\ ss}$, $C_{max\ ss}$) and area under the concentration time curve from time zero to time=t and time=24 hours ($AUC_{0\text{-}t,}$ $AUC_{0\text{-}24}$) after administration of ZX008 derived using a population pharmacokinetic model.

Sample Size Determination:
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 the frequency of drop seizures that is at least 30 percentage points lower than adding placebo to current therapy. The variability expected in the trial was estimated from the confidence intervals reported in a Phase 3 trial of clobazam for patients with Lennox-Gastaut syndrome (Ng 2011) leading to an assumption that the SD is 50%. Under these assumptions, and using a Wilcoxon rank-sum test to approximate the primary analysis, a sample size of 63 subjects per treatment group 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 16 subjects per group for a total of 79 subjects per treatment group. 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. The sample size of 10 to 15 subjects per treatment group in Cohort B is expected to provide a descriptive assessment of whether the treatment effect in Japanese subjects is similar to that observed in Cohort A subjects from the rest of the world.

Statistical Methods:
Part 1
The primary analyses of the study will be performed on data from Part 1 Cohort A after the last subject enrolled in Cohort A has completed the last study visit of Part 1. A secondary analysis will be conducted after the last Cohort B subject has enrolled and completed the last study visit of Part 2. Analysis results for Part 1 from Cohort A and Cohort B will be compared through descriptive statistics, and if reasonable, some analyses may be performed using data from Cohort A and Cohort B combined. Subjects randomized to 0.5 mg/kg/day (ie, those taking concomitant STP) will be grouped with subjects randomized to 0.8 mg/kg/day for all efficacy analyses.

Efficacy
Primary Efficacy Analysis: The primary efficacy endpoint for Part 1 is the percent change in frequency of seizures that result in drops (DSF: drop seizure frequency) per 28 days between the T+M and Baseline periods in Cohort A. The DSF will be calculated from all available data collected during the Baseline and treatment periods without imputation. The percent change in DSF will be calculated as the change in DSF between T+M and Baseline / DSF during Baseline× 100. Both the mean and median percent change in DSF will be presented. The primary endpoint will be assessed using a non-parametric rank analysis of covariance (ANCOVA) with treatment and weight group as factors, rank baseline DSF as a covariate, and rank percent change in DSF from baseline as the response variable. The primary analysis will compare the ZX008 0.8 mg/kg/day group to the placebo group at the alpha=0.05 level of significance. The difference between the ZX008 0.8 mg/kg/day and placebo groups in percent change in DSF, and its 95% confidence interval, will be estimated using the Hodges-Lehmann method. As a sensitivity analysis, the primary endpoint will also be analyzed using a parametric ANCOVA that incorporates treatment group and weight group as factors, log baseline DSF as a covariate; and log DSF during T+M as the response variable. Another sensitivity analysis will use a Wilcoxon rank-sum test to compare the ZX008 0.8 mg/kg/day group to the placebo group. Part 1 Cohort B will be analyzed using analogous methods.

A key secondary analysis will compare the ZX008 0.2 mg/kg/day group to the placebo group on percent change in DSF using the same method as the primary analysis. Other key secondary analyses will compare the ZX008 0.8 and 0.2 mg/kg/day groups to the placebo group on the proportion of subjects who achieve a ≥50% reduction from baseline in DSF. The analyses will utilize independent logistic regression models that incorporate the same factors and covariate as the primary analysis. Two other key secondary analyses will compare both ZX008 dose groups (independently) to placebo on the proportion of subjects assessed by the Principal Investigator as minimally, much, or very much

improved on the Clinical Global Impression – Improvement (CGI-I). The comparisons will employ separate Cochran-Mantel-Haenszel tests (CMH) stratified by weight strata. A serial gatekeeper strategy will be used to maintain the Type 1 error rate at α=0.05 across the family of analyses that support the primary and key secondary objectives.

Safety

All safety data will be appropriately analyzed by treatment group. The number and percentage of subjects with AEs will be displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries in terms of severity and relationship to study drug will also be provided. Adverse Events of Special Interest (AESI) and Serious AEs (SAEs) will be summarized separately in a similar manner. Laboratory tests, vital signs, physical examinations, neurological examinations, ECG, Doppler echocardiogram, chest x-ray (France and Netherlands only), EEG (Italy only), C-SSRS, Tanner Staging results, etc., will be summarized appropriately, by treatment. All safety summaries will be based on the Safety Population.

Pharmacokinetics

Model derived plasma PK parameters (C_{max_ss}, $Cmin_{\_ss}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$) will be summarized descriptively by treatment group, when sufficient data are available. A Population pharmacokinetic (PopPK) model of fenfluramine, previously developed using data from healthy adults and pediatric patients with Dravet syndrome, will be updated to include the fenfluramine and norfenfluramine concentration-time data collected during the Maintenance Period of Part 1. This model will be informed by all relevant data available at the time of data collection (both adults and pediatrics). The population mean and interindividual variability estimates from the fit of the PopPK model will be summarized. The results from the PopPK modeling will be reported separately and conducted according to a separate SAP.

Part 2

The primary objective of Part 2 is to assess the long-term safety and tolerability of ZX008 in children and adults with LGS with regard to AEs, laboratory parameters, physical examination, neurological examination, vital signs, ECG, ECHO, body weight, and BMI.

The number and percentage of subjects who experience treatment emergent AEs will be displayed by preferred term using MedDRA. Summaries in terms of severity and relationship to study drug will also be provided. SAEs will be summarized separately in a similar manner. Laboratory tests, vital signs, physical examinations, neurological examinations, ECG, ECHO, chest x-ray (France and Netherlands only), EEG (Italy only), cognition and body weight will be summarized using appropriate methods.

Effectiveness will be assessed by the change from baseline (prior to randomization into Part 1) in DSF. The DSF per 28 days will be calculated as the number of seizures that result in drops divided by the number of days in the period and multiplied by 28. The change in DSF during the Part 2 OLE Treatment Period will be calculated as the difference between DSF during the OLE and the baseline DSF measured prior to randomization in Part 1. Both the mean and median percent change in DSF will be presented and the statistical significance of the percent change will be assessed using a Wilcoxon signed-rank test. Other secondary assessments will be compared to baseline from prior to Part 1, or by visit throughout Part 1 and Part 2, as appropriate.

Table 1. Schedule of Assessments: Part 1

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**
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		
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	

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**
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		
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]

Abbreviations: AED=antiepileptic drug; BMI=body mass index; C=Collect; CBD=cannabidiol; D=Dispense; ECG=electrocardiogram; 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.

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

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.
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.

Table 2. Schedule of Assessments: Part 2

Study Assessments – PART 2	**OLE Treatment Period****					**Post-Dosing**	**Cardiac Follow-up**
Visit Number	**Visit 15[a]**	**Visit 16[b]**		**Visits 17-21 (Months 1, 2, 3, 6 and 9**)**	**Visit 22[c] (EOS/ET) Month 12**	**Visit 23**	**Visit 24 and 25**
OLE Study Day	**1[a]**	**15**		**30, 60, 90, 180, and 270**	**365**	**379[k,q]**	**(3-24 months post last dose)[d, k]**
		Clinic	**Phone**				
Informed Consent	X						
Entry Criteria	X						
Demographics	X[a]						
Medical/Neurological History	X[a]						
Epilepsy History	X[a]						
Physical Examination, complete	X[a]				X		X
Physical Examination, abbreviated		X[m]		X[m]		X[m]	X
Neurological Examination, complete	X[e]				X		
Neurological Examination, abbreviated		X[m]		X[m]		X[m]	
Vital signs	X	X		X	X		
Weight	X[a]	X		X	X	X	
Height	X[a]				X		
12-lead ECG	X[a]			X	X		X
Doppler ECHO	X[a]			X[f,g]	X		X
EEG (Italy only)	X			X[p]	X		
Chest x-ray (France, Netherlands only)					X		X
Urine or Serum Pregnancy Test[h]	X[a]			X[n]	X		
Clinical laboratory evaluation (hematology/chemistry/urinalysis[r], etc.)	X[i]	X[i]		X[n]	X		
Whole blood CBD/ THC Panel	X[a]			X[n]	X		
Plasma sample for background AEDs		X[m]		X[n]	X		
Tanner Staging (for subjects >7 to 18 years old)	X[a]			X[j]	X		
C-SSRS	X[a]			X	X		
CGI-I (assessed by parent/caregiver)	X[a]			X	X		
CGI-I (assessed by Principal Investigator)	X[a]			X	X		
HADS (Effect of parent/caregiver)	X[a]			X[o]	X		
BRIEF	X[a]			X[o]	X		
QOLCE	X[a]			X[o]	X		
Zarit Burden	X[a]				X		
Subject Diary	C/R/D	C/R/D	R	C/R/D	C/R/D	C/R	
Study Medication	D	C/R	R	C/R/D	C/R/D[k]	C/R	
Review Daily Diary Completion	---------- X ----------						
Concomitant Medication	X[a]	----------X----------					
Adverse Events	X[a]	----------X----------					

Study Assessments – PART 2	**OLE Treatment Period****				**Post-Dosing**	**Cardiac Follow-up**
Visit Number	**Visit 15[a]**	**Visit 16[b]**	**Visits 17-21 (Months 1, 2, 3, 6 and 9**)**	**Visit 22[c] (EOS/ET) Month 12**	**Visit 23**	**Visit 24 and 25**
Adverse events of special interest	X[a]	----------X----------				X[l]

Abbreviations: AED=antiepileptic drug; BMI=body mass index; C=Collect; CBD=cannabidiol; D=Dispense; ECG=electrocardiogram; 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

a: Use data collected at Visit 12 of Part 1.
b: At the discretion of the Investigator, Visit 16 may be conducted as a phone visit.
c: Or early termination.
d: Safety Follow-up visits will be conducted for subjects who terminate early from Part 2 and for those who complete Part 2. Standard follow-up visits should occur 3 and 6 months after the last dose. For subjects enrolled in Germany, France and Netherlands, follow-ups will also occur 24 months after the last dose. If there are any findings at a post-dose follow-up, a follow-up visit will be scheduled every 3 months until resolved or stabilized.
e: Use Part 1 Visit 12 information unless complete neurological examination is warranted based on significant changes in subject status.
f: ECHOs will be performed at Months 1, 3, 6, and 9.
g: The Months 3, 6, and 9 ECHO may be performed any time within 3 weeks prior to the study visit. If a subject discontinues early from the study, the ECHO should be scheduled as soon as practical.
h: Females of child-bearing potential
i: For Visit 15, use data collected at Part 1 Visit 12 unless clinical laboratory evaluation is warranted based on significant changes in subject status. For Visit 16, clinical laboratory evaluation is optional based on subject status.
j: Visit 20 only.
k: For subjects who are entering a different open-label trial for ZX008, do not initiate drug taper or conduct post-dosing and cardiac follow-up visits.
l: Only adverse events related to cardiac safety will be collected at this visit.
m: An abbreviated physical and/or neurological examination to be conducted as appropriate based on last exam and reported AEs.
n: Visits 19, 20, and 21 (Months 3, 6, and 9) only.
o: Visit 20 (Month 6) only
p: For subjects enrolled in Italy only: conduct routine EEG during Visits 15, 19, and 22
q: Visit 23 may be conducted as a phone call if physical and neurological examinations are not clinically indicated, provided diaries and study medication are returned by this time.
r: Urine for urinalysis may be collected at home, the night before the clinic visit, as long as collection procedures are followed to maintain sample stability.

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

1. INTRODUCTION

1.1. BACKGROUND INFORMATION ON INDICATION STUDIED

ZX008 (fenfluramine hydrochloride) is under clinical development for the adjunctive treatment of patients with Lennox-Gastaut syndrome (LGS).

LGS is a rare epileptic encephalopathy. Onset of LGS usually occurs most commonly before age 11, with a peak between 3 and 5 years of age (Arzimanoglou 2009; Hancock 2013). Patients with LGS account for 5–10% of children with seizures (Panayiotopoulos 2005). The diagnosis of LGS includes clinical signs combined with typical EEG features. The clinical presentation of LGS is heterogeneous, however LGS is always characterized by a triad of symptoms: multiple seizure types, slow spike-and-wave EEG, and abnormal cognitive development. The most common seizure types are generalized tonic-clonic seizures, tonic seizures, atonic seizures, and tonic/atonic seizures, all of which most often can result in "drop attacks." Other seizure types that occur in some LGS patients include atypical absences, nonconvulsive seizures, focal seizures, and myoclonic seizures. Nearly all LGS patients have treatment-resistant, lifelong epilepsy. Prognosis for LGS is very poor: 5% of children die, 80% to 90% continue having seizures into adulthood, and nearly all have cognitive and behavioral problems (Panayiotopoulos 2005). Children and adults with LGS have an enormous impact on their families, and efforts to improve the quality of life for these patients are complex.

1.1.1. Existing Treatment for LGS

Currently, there are 7 approved anti-epileptic drug (AED) products for LGS in the US: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, and cannabidiol (Epidiolex®). Two AEDs are approved in Japan for the treatment of LGS: lamotrigine (2008) and rufinamide (2013). Nine AEDs are approved for the treatment of LGS in Europe: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, valproate, nitrazepam, and cannabidiol (Epidyolex®). Other pharmacologic (valproate, benzodiazepines, zonisamide) and nonpharmacologic (KD, VNS, surgery) treatments also are prescribed based on clinical experience.

Because patients with LGS experience a range of different seizure types, the condition is notoriously difficult to treat (Arzimanoglou 2009, Cross 2017) and seizures in LGS are usually not fully controlled (Hancock 2013). Initial treatment for LGS is usually monotherapy with one of the currently approved AEDs. If this is not successful, which is the most common case, a second agent is usually added; although some physicians move on to the second drug as monotherapy (Wheless 2007; Arzimanoglou 2009). The treatment of LGS frequently requires a combination of 2 or more of these compounds, but with continued suboptimal seizure control. The recommendation is to attempt to use drugs that have different mechanisms of action and the least amount of interaction with one other. After lack of response to 2 or more AEDs, nonpharmacological treatments such as KD, VNS, or surgery may be considered. A treatment that has been shown to be effective in common certain seizure types cannot be assumed to be effective in patients with LGS to treat that seizure type.

Given the suboptimal treatment of seizures in the majority of LGS patients, even with polytherapy, and the developmental and cognitive consequences believed to be caused, at least in

part, by frequent childhood seizure activity, there is a medical need for a new anticonvulsant treatment with a novel mechanism of action that can significantly reduce seizure activity in LGS.

1.2. BACKGROUND INFORMATION ON STUDY PRODUCT

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

Fenfluramine was introduced in the USA in 1973. Products containing fenfluramine and D- fenfluramine were withdrawn from all markets between 1997 and 2000 after reports of heart valve disease and pulmonary hypertension (Connolly 1997; CDC 1997; Wong 1998). While the risk/benefit relationship for fenfluramine is thus considered unfavorable for the treatment of obesity in adults, establishing seizure control in LGS or any of the refractory catastrophic childhood epilepsies might lead to a more acceptable risk/benefit profile for fenfluramine.

As a result of this previous extensive use of fenfluramine, there is a large body of information in the public domain concerning its pharmacology, toxicology and use in the treatment of obesity. These data are summarized in the ZX008 Investigator Brochure (ZX008 IB). There is also a large body of information concerning its clinical safety profile.

1.3. CLINICAL DATA

Two double-blind, placebo-controlled, randomized Phase 3 studies (Study 1 and Study 1504 Cohort 2) of ZX008 in children and young adults with DS have been completed. Study 1 investigated two doses (0.2 and 0.8 mg/kg/day) of ZX008 or placebo and included 119 subjects with Dravet syndrome from North America, Europe and Australia. Study 1504 Cohort 2 included 87 subjects from North America and Europe, and compared addition of ZX008 (0.5 mg/kg/day) or placebo in subjects who were receiving standard of care anti-epileptic treatments where administration of STP was mandatory.

The primary efficacy measure in both studies was the change from baseline in the frequency of convulsive seizures (per 28 days) during the combined 14-week (Study 1) or 15-week (Study 1504 Cohort 2) Titration and Maintenance periods (T+M). The primary analysis in Study 1 compared ZX008 0.8 mg/kg/day to placebo and in Study 1504 Cohort 2 compared ZX008 0.5 mg/kg/day to placebo. A key secondary measure in Study 1 compared the 0.2 mg/kg/day group to the placebo group on the same measure. Other key secondary measures in both studies included a comparison of the ≥ 50% Responder Rate (ie, the number of subjects with a ≥ 50% reduction in the frequency of convulsive seizures), and the longest seizure free interval.

Both Study 1 and Study 1504 Cohort 2 met the primary endpoint with a highly statistically significant reduction in convulsive seizures in all active treatment groups.

In Study 1, subjects randomized to ZX008 0.8 mg/kg/day and 0.2 mg/kg/day had a median baseline convulsive seizure frequency of 20.7 and 17.5, respectively, compared to 27.3 for subjects randomized to placebo. Subjects randomized to ZX008 0.8 mg/kg/day (n= 40) achieved a 62.3% greater reduction in mean monthly convulsive seizure frequency (P<0.001) compared to those in the placebo group (n=40). In addition, subjects randomized to ZX008 0.2 mg/kg/day (n=39) had a 32.4% reduction compared to placebo (P = 0.021). Comparing the seizure reduction results for the 2 doses of ZX008 in Study 1 suggests a dose-response effect on seizures. The pattern of individual responses in the ZX008 0.2 mg/kg/day group supports the selection of 0.2 mg/kg/day as the minimally effective dose.

In Study 1504 Cohort 2, subjects randomized to ZX008 0.5 mg/kg/day had a median baseline convulsive seizure frequency 14.0 compared to 10.7 for subjects randomized to placebo. Subjects randomized to ZX008 0.5 mg/kg/day achieved a 54.0% reduction compared to placebo (P < 0.001).

Controlling for multiplicity with a hierarchical testing procedure, all key secondary endpoints were met in both studies, for ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups (Study 1) and ZX008 0.5 mg/kg/day (Study 1504 Cohort 2). In Study 1, the proportion of subjects achieving a ≥ 50% reduction from Baseline in CSF was 67.5% for the ZX008 0.8 mg/kg/day group, and 38.5% for the 0.2 mg/kg/day group, with both groups being statistically significantly different from placebo (12.5%; P < 0.001 and P = 0.009, respectively). In Study 1504 Cohort 2, 53.5% of subjects randomized to ZX008 0.5 mg/kg/day compared to 4.5% of subjects randomized to placebo achieved a ≥ 50% reduction from Baseline in CSF (P <0.001).

The proportion of subjects with a ≥ 50% reduction in monthly convulsive seizure frequency was also highly statistically significant for all ZX008 dose groups compared to placebo, with 38.5%, 53.5%, and 67.5% of subjects in the 0.2 mg/kg/day, 0.5 mg/kg/day, and 0.8 mg/kg/day cohorts achieving ≥ 50% reduction as compared to 8.3% in placebo. Additionally, in Study 1, subjects randomized to ZX008 0.2 and 0.8 mg/kg/day had a median 15- and 25-day convulsive seizure-free interval, respectively, compared to 9.5 days for placebo (P = 0.035 and P < 0.001). In Study 1504 Cohort 2, subjects randomized to ZX008 0.5 mg/kg/day had a median 22-day convulsive seizure-free interval compared to 13 days for placebo (P < 0.004).

ZX008 was generally well tolerated in both Study 1 and Study 1504 Cohort 2. Though more subjects randomized to ZX008 than to placebo reported TEAEs during the double-blind studies, the percent of subjects with serious TEAEs was similar. Additionally, the adverse events observed in the program were either already known to be associated with fenfluramine, are common to many other antiepileptic drugs being prescribed to these patients, and/or are common to the age group and population studied. Specifically, the most common adverse events seen were diarrhea, fatigue, pyrexia, upper respiratory tract infection, blood glucose decreased, weight decreased, decreased appetite, lethargy and tremor. No valvular heart disease, pulmonary arterial hypertension or abnormal valve structure was observed in any subject at any time during the entire program.

In an integrated analysis of safety of the double-blind studies, 117 (95.9%) subjects in any ZX008 treatment group and 68 (81.0%) subjects in the combined placebo group reported at least 1 TEAE. The most common (≥ 10%) TEAEs reported in subjects receiving any dose of ZX008

were: blood glucose decreased, constipation, decreased appetite, diarrhea, echocardiogram abnormal, fall, fatigue, lethargy, nasopharyngitis, pyrexia, seizure, somnolence, status epilepticus, tremor, upper respiratory tract infection, vomiting, and weight decreased. All of the echocardiogram abnormal TEAEs were trace mitral or trace aortic valve regurgitation, which are normal physiological findings seen in healthy children (Webb 2015). Fifteen (12.3%) subjects in any ZX008 treatment group and 11 (13.1%) subjects in the combined placebo group reported at least 1 serious TEAE. The most frequently reported (≥ 5%) serious AEs (SAEs) were status epilepticus and seizure. A total of 76 (62.3%) subjects in any ZX008 treatment group and 22 (26.2%) subjects in the combined placebo group reported a TEAE determined by the Investigators to be related to the study drug, and 3 (2.5%) subjects in any ZX008 treatment group and 1 (1.2%) subject in the combined placebo group reported a serious TEAE determined to be related to the study drug. During the double-blind treatment periods, 7 (5.7%) subjects in any ZX008 treatment group and 1 (1.2%) subject in the combined placebo group reported a TEAE that lead to discontinuation from study participation. There were no deaths during the double-blind treatment periods.

Subjects in Study 1 and Study 1504 if eligible could participate in Study 1503, an open-label long-term, safety extension study that is currently ongoing. All subjects in Study 1503 started ZX008 at 0.2 mg/kg/day and could flexibly titrate to a maximum dose of 0.8 mg/kg/day, maximum 30 mg/day (if not receiving a concomitant STP regimen) or 0.5 mg/kg/day, maximum 20 mg/day (if receiving concomitant STP regimen), based on effectiveness, safety and tolerability. Though primarily a safety study, subjects in Study 1503 maintained a daily seizure diary and continued to complete rating scales on overall effectiveness and quality of life measures.

In a safety update of Study 1503 (cut-off date 14-Oct-2019, n=330 enrolled), the median percent change in CSF compared to baseline (core study) for the overall open-label Treatment period (Day 1 to End of Study [EOS]) was -66.8% (P <0.001). The reduction from baseline in monthly CSF observed at Month 1 of the open-label Treatment period was maintained through Month 24, the longest treatment duration included in the analysis. A total of 317/330 subjects reported at least 1 TEAE during the open-label Treatment period. The most common (≥ 10%) TEAEs reported during the open-label Study 1503 at the time of the cut-off date were blood glucose decreased, decreased appetite, diarrhea, ear infection, echocardiogram abnormal, influenza, nasopharyngitis, pyrexia, seizure, and upper respiratory tract infection. As in the double-blind studies, all of the echocardiogram abnormal TEAEs in Study 1503 were trace mitral or trace aortic valve regurgitation, which are not considered pathologic as stated in current guidelines on the use of ECHO for the assessment of valve function (Zoghbi 2017, Lancellotti 2010a, Lancellotti 2010b). At least 1 treatment-emergent SAE was reported by 80/330 (24.2%) subjects. The most frequently reported (≥ 5%) SAE was seizure, occurring in 24/330 (7.3%) of subjects. A total of 176/330 subjects (53.3%) experienced at least 1 TEAE that was considered to be related to study treatment and 8/330 subjects (2.4%) reported at least 1 SAE that was considered to be related to study treatment. A total of 11/330 (3.3%) subjects discontinued due to a TEAE.

Please reference the ZX008 IB for more detailed information on the safety and efficacy of ZX008.

1.4. PHARMACOKINETICS, PRECLINICAL DATA, AND CLINICAL PHARMACOLOGY

1.4.1. Pharmacokinetics

The pharmacokinetics of fenfluramine, norfenfluramine and their respective isomers have been studied in mice, rats, dogs and humans. Fenfluramine and norfenfluramine were more slowly eliminated in humans than in other species. In vitro metabolism studies have shown considerable species differences in the metabolism of fenfluramine, with no single species having a profile similar to humans. No human-specific metabolites were detected, and both rat and dog showed good coverage of the human fenfluramine metabolites. In humans, fenfluramine is metabolized primarily to norfenfluramine. Fenfluramine is partially metabolized by CYP1A2, CYP2B6, and CYP2D6, with additional metabolism by CYP2C9, CYP2C19, and CYP3A4. Norfenfluramine does not appear to be strong substrate of any CYP450 enzyme, but is metabolized by CYP1A2, CYP2B6, CYP2C19, and CYP2D6 in vitro. There is also some contribution of renal clearance to the elimination of dexfenfluramine (8%-16%) and nordexfenflurmaine (7%-8%) from the body. Because fenfluramine and its active metabolite norfenfluramine have multiple pathways of elimination, interference with a single pathway is unlikely to cause a significant change in fenfluramine's clearance though the probability of an interaction increases if multiple elimination mechanisms are affected simultaneously.

While in vitro studies showed that both fenfluramine and norfenfluramine cause weak inhibition of CYP2D6 and fenfluramine causes weak induction of CYP3A4 and CYP2B6, further analysis based on the FDA's mechanistic static model shows that fenfluramine and its major metabolite norfenfluramine are unlikely to alter the pharmacokinetics of substrates of CYP450 enzymes in the range of ZX008 doses that will be administered in this study.

In Study 1 and Study 1504 Cohort 2, pharmacokinetic parameters of fenfluramine and norfenfluramine for patients with Dravet syndrome were determined using a population pharmacokinetic (PopPK) model developed using PK data from both healthy volunteers and patients with Dravet syndrome. These data are provided in Table 3.

Table 3: Post Hoc Estimates of Fenfluramine and Norfenfluramine Steady-State Pharmacokinetic Parameters in Subjects with Dravet Syndrome in Study 1 (Geometric Mean [CV%])

Analyte:	**Fenfluramine**		**Norfenfluramine**	
ZX008 Dose	**0.2 mg/kg/day**	**0.8 mg/kg/day**	**0.2 mg/kg/day**	**0.8 mg/kg/day**
C_{max} (ng/mL)	18.5 (29.1)	68.0 (40.7)	9.60 (52.8)	37.8 (49.9)
AUC_{0-24} (ng.hr/mL)	375 (32.9)	1390 (43.5)	220 (55.5)	872 (52.1)
T_{max} (hr) Median (Min, Max)	3.00 (3.00 to 3.50)	3.00 (3.00 to 3.50)	4.00 (3.50 to 5.00)	4.50 (3.50 to 5.00)

Source: ICPD Report 00445-3, Table 5.
Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours; BID = twice daily; C_{max} = peak plasma drug concentration; CV= coefficient of variation; Max = maximum; Min = minimum; T_{max} = time of peak plasma drug concentration.

1.4.2. Preclinical Data

In a GLP compliant 10-week juvenile toxicology and toxicokinetic study in rats, which included fenfluramine hydrochloride doses of 3.5, 9 and 20 mg/kg/day by oral gavage for 10 weeks (Days 7 to 76 postpartum). The data from the juvenile toxicology studies suggest that the effects of fenfluramine in juvenile animals (CNS-related clinical signs, effects on body weight and food consumption, and neurobehavioral deficits) are similar to effects previously reported in neonatal and adult rats (Morford 2002; Williams 2002). There was no evidence of CNS histopathology; importantly, there were also no histopathologic findings in aortic or mitral cardiac valves, and no adverse effects on any other tissues at necropsy.

The NOAEL for the juvenile rats was determined to be 9 mg/kg/day. A NOAEL of 9 mg/kg/day corresponds to PND 76 AUC0-t of 3480 hr*ng/mL for males and 4680 hr*ng/mL for females for fenfluramine, and 4470 hr*ng/mL for males and 6210 hr*ng/mL for females for norfenfluramine. The AUC(0-t) at the NOAEL provided a safety factor (both sexes combined) of approximately 3-fold or higher for fenfluramine and approximately 6-fold or higher for norfenfluramine.

1.4.3. Clinical Pharmacology

Please see the ZX008 IB for details on clinical pharmacology. Below are the clinical pharmacology conclusions.

- Coadministration of ZX008 with the STP regimen (STP with CLB and/or VPA) resulted in an increased fenfluramine and decreased norfenfluramine concentrations, and therefore a dose adjustment is used in the clinical trials.
- STP is the predominant perpetrator of the interaction; while VPA and CLB do not have a significant independent impact on the PK of fenfluramine or norfenfluramine, whether administered with or without STP.
- Coadministration of ZX008 with CBD at steady state resulted in increased fenfluramine concentrations but this increase was within the range of safe dosing used in Study 1504 Cohort 2; thus, no dose adjustment is recommended when fenfluramine is coadministered with CBD.
- In the population PK analysis, intrinsic patient factors (age, gender, race/ethnicity, and BMI) demonstrated no substantial impact on the clearance or exposure to fenfluramine or norfenfluramine when dosed on a mg/kg basis to a maximum of 30 mg/day.
- ZX008 had no effect on QTc intervals at either the therapeutic or supratherapeutic dose, and no relationship was observed between fenfluramine or norfenfluramine exposure and QTcF.
- ZX008 exhibited approximately dose proportional PK over a 4-fold range of doses (15 to 120 mg/day).

- CYP450 metabolizer genotype for CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 had no impact on the PK of fenfluramine or norfenfluramine.

Further details on the nonclinical data of ZX008 are available in the Investigator's Brochure (ZX008 IB). The current version is available in the Investigator Study File.

1.5. BACKGROUND INFORMATION ON REFERENCE PRODUCT

Not applicable.

1.6. RATIONALE FOR CURRENT STUDY

There have been several published reports of fenfluramine's successful treatment of refractory childhood epilepsy in the 1980s (Aicardi 1985; Aicardi 1988) and its successful treatment of 11 refractory pediatric epilepsy patients in Belgium (Boel 1996).

A number of small studies and case series have been published describing the use of fenfluramine in epilepsy. In 1996, a Belgian group reported on the use of fenfluramine in 11 children (ages 18 months to 15.5 years old) with refractory or self-induced epilepsy (Boel 1996). Patients were treated with fenfluramine at 0.5 – 1 mg/kg/day for 3 to 8.5 years (average duration 5 years 7 months). Seven children (64%) became seizure-free and the remaining 4 patients experienced ≥75% reduction in seizure frequency.

In 2002, Casaer and Boel published a brief update of their study with fenfluramine. The study population was expanded to 22 patients with intractable or self-induced seizures, including the previously reported 11 patients (Casaer 2002). The duration of treatment was between 1 and 12 years. In this study, of the 22 patients treated, 6 (27%) became seizure-free, 10 (45%) patients had a 90% reduction in seizure frequency and 6 (27%) patients were nonresponders.

Fenfluramine was also shown to be effective in multiple seizures types in Dravet syndrome, another drug resistant pediatric epileptic encephalopathy syndrome (Ceulemans 2012; Schoonjans 2015; Ceulemans 2016; Schoonjans 2017). Zogenix is currently evaluating ZX008 in Dravet syndrome in two Phase 3 double-blind, randomized, placebo-controlled studies and one open-label extension (clinicaltrials.gov identifiers: NCT02826863, NCT02682927, and NCT02823145).

Currently, a small cohort of refractory patients with Lennox-Gastaut syndrome in Belgium are being treated in an ongoing Phase 2 open-label, pilot, dose-finding trial of fenfluramine as an add-on therapy to conventional therapy (Lagae 2017; Study S58545; clinicaltrials.gov identifier: NCT02655198).

The study includes a 20-week Core period, in which subjects are titrated to ≥50% response and then held at that dose until the end of the 20-week period, and an Extension period, in which subjects are titrated to maximum efficacy and tolerability. Subjects aged 3 to 18 years, fulfilling the diagnostic criteria for LGS as described by the ILAE in 1989, who have failed at least two AEDs (including VNS), and have had at least 4 documented convulsive seizures (generalized tonic-clonic, tonic seizures, atonic seizures, and focal seizures with a motor component) and on at least two AEDs at stable doses in the prior 4 weeks are eligible for this study. After the initial 4-week baseline period to record seizure type and frequency, treatment with fenfluramine, 0.2 mg/kg/day, is initiated. An efficacy response ("responder") is defined as a ≥50% reduction in

major motor seizure frequency (GTC+TS+AS+FS). At the 8-week visit (following 4 weeks of ZX008 treatment), subjects who were nonresponders and have no intolerable side effects receive an increased dose of 0.4 mg/kg/day. At the 12-week visit, subjects who were nonresponders and have no intolerable side effects receive an increased dose of 0.8 mg/kg/day. At any visit, subjects who achieve a ≥50% reduction in major motor seizure frequency remain at their currently administered dose. As this is a pilot dose-finding study, it is important to note that per protocol, dose escalation stops when a subject's convulsive seizure frequency is reduced by ≥50% of baseline. It is possible that a higher dose could result in even greater seizure reduction. The maximum allowed dose is 30 mg/day.

Results have been presented for the 13 LGS subjects who completed the Core study: (Lagae 2017). Overall, subjects had received a median of 8 years of antiepileptic treatment and were failing a median of 5 AEDs prior to entry. Upon study entry, patients were taking a median of 4 concurrent anti-epileptic therapies. All subjects received ZX008 treatment for at least 20 weeks with the exception of 3 subjects who discontinued due to lack of efficacy; of which 2 also discontinued due to side effects. For subjects who completed the 20-week Core period, the median seizure frequency was reduced from a mean of 60 major motor seizures per month in the pre-ZX008 baseline period to a mean of 22 major motor seizures per month at the end of the Core ZX008 treatment period. At week 20, 8 of the 13 enrolled patients (62%) had at least a 50% reduction in major motor seizures with ZX008 treatment, and three (23%) patients had at least a 75% reduction. Nine of the 13 patients completed the Core period and entered the Extension period. At the time of each of subjects' most recent visit, 6 of 9 patients (67%) had at least a 50% reduction in major motor seizures and 2 of 9 (22%) had a 75% or greater seizure reduction. In the Extension period, there was a 58% median reduction in seizure frequency as compared to baseline. The most common treatment emergent adverse events to date include decreased appetite (n=4) and decreased alertness/fatigue (n=3). Sleep problems, tiredness, and sleepiness were each reported in one subject.

No clinical signs of valvulopathy or pulmonary hypertension have been observed in any patients in the Belgian cohort (ZX008 IB0).

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

Prior to being withdrawn from the market, fenfluramine was marketed at doses of 20 mg and 40 mg three times daily for the management of obesity in adults. The doses tested thus far in Dravet syndrome range from 0.12 to 0.9 mg/kg/day in subjects over 1 year of age to adults in the Belgian cohort, and 0.2 and 0.8 mg/kg/day in the Zogenix Phase 3 trials. Doses tested in pediatric studies evaluating autism and ADHD ranged from 0.65 mg/kg/day to 3.6 mg/kg/day, but a commonly used dose was 1.5 mg/kg/day. Occasionally, fixed doses of 30 to 80 mg were used. The PK exposure associated with the doses in the LGS study of 0.2 mg/kg/day and 0.8 mg/kg/day, administered orally (in equally divided doses BID) is lower than that obtained at the doses used in the past for the treatment of obesity in adults and of neurobehavioral conditions in children and adolescents (ZX008 IB). The doses used in this study are based on the data from the DS and LGS patients being successfully treated in Belgium discussed above.

In summary, fenfluramine has been shown to be effective in reducing the frequency of seizures in patients with Dravet syndrome and LGS, and its activity persists over a long duration of time (Ceulemans 2012, Ceulemans 2016, Schoonjans 2017, Lagae 2018). Though the mechanism remains to be fully elucidated, data from in vitro receptor binding, functional assays, and zebrafish models suggest that fenfluramine reduces seizures by acting as an agonist at the 5-HT1D and the 5-HT2C receptors and by acting on the sigma-1 receptor. Fenfluramine may also exert anti-seizure activity through the 5-HT1A and the 5-HT2A receptors (ZX008 IB).

The lack of consistent efficacy and individual tolerability and safety concerns with current treatments available for LGS have resulted in the continued significant unmet need for a new treatment with a novel mechanism of action for children and adults with LGS.

1.7. RISK-BENEFIT ASSESSMENT

As described above, fenfluramine has been used successfully for up to 30 years in Belgium in refractory pediatric epilepsy patients, including those with LGS and DS (Boel 1996, Ceulemans 2012, Schoonjans 2015, Schoonjans 2017). The doses tested thus far in DS range from 0.12 to 0.9 mg/kg/day in subjects over 1 year of age to adults. No patients have developed valvulopathy or pulmonary hypertension.

The clinical benefit of ZX008 in the Lennox-Gastaut syndrome has been evaluated in an open label study (Lagae 2017, Lagae 2018) as mentioned in Section 1.6. In addition, 2 positive, adequate and well-controlled, multi-national, randomized, double-blind, placebo-controlled trials of ZX008 in subjects with Dravet syndrome, Study 1 and Study 1504 Cohort 2, demonstrated a statistically significant and clinically meaningful reduction in monthly convulsive seizure frequency and was generally well tolerated. There was no clinical or echocardiographic evidence of cardiac valvulopathy or pulmonary hypertension in any study, and no patient discontinued participation or required a change in monitoring in the study due to cardiac factors. The PK exposure associated with the doses of ZX008 in the DS studies of 0.2 mg/kg/day to 0.8 mg/kg/day administered orally [in equally divided doses twice per day (BID)] is lower than that obtained at the doses used in the past for the treatment of obesity in adults and of neurobehavioral conditions in children and adolescents (ZX008 IB). The doses used in this study are based on the data from the patients being successfully treated in Belgium discussed above, Study 1, and Study 1504 Cohort 2 data.

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

The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and should detect expected and unexpected treatment-emergent adverse events, and are the same as those currently being utilized for the global Phase 3 DS program.

The approximate volume of blood (158.0 mL) planned for collection from each subject over the course of the entire study (Screening to End of Study Part 2, but not including repeat or additional tests ordered by the Investigator) presents no undue risk to the subjects.

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

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. PART 1

2.1.1. Primary Objective

The primary objective of Part 1 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 between baseline and the combined Titration and Maintenance Periods (T+M).

2.1.2. Key Secondary Objectives

The key secondary objectives of Part 1 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 frequency of seizures that result in drops between baseline and 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 rating, as assessed by the Principal Investigator.

See Statistical Methods (Section 10.1.6.1) for hierarchical testing procedure.

2.1.3. Additional Secondary Objectives

Additional secondary objectives 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 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 [AS], tonic/atonic seizures [TA], clearly recognizable focal seizures [FS], and myoclonic seizures [MS] that result in a drop).
  - Change in the frequency of all countable seizures (ie, motor and nonmotor) between baseline and T+M
  - Change in frequency of seizures that 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
  - 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
  - Number of seizure-free days, defined as 1) days with no countable seizures and 2) days with no seizures that result in drops
  - Longest interval between 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 rating, as assessed by the parent/caregiver.

2.1.4. Safety Objective

The safety objectives of Part 1 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 BMI
- To evaluate the change from baseline in cognition using age-appropriate versions of the BRIEF

2.1.5. Pharmacokinetic Objective

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.

2.1.6. 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 frequency of rescue medication usage
  - The incidence of medical services to treat seizures
  - The incidence of status epilepticus.
  - The change from baseline in behavior using the Vineland Adaptive Behavior Scale (VABS)
  - The change from baseline in 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)

2.2. PART 2

2.2.1. Primary Objective

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

2.2.2. Secondary Objectives

The secondary objectives of Part 2 are:

- To assess the effect of ZX008 relative to the baseline on the following effectiveness measures:
  - The change in the frequency of seizures that result in drops
  - The change in the frequency of all countable motor seizures (GTC, TS, CS, AS, TA, FS, MS with a drop)
  - The change in the frequency of all countable seizures
  - 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) in frequency of all countable seizures that result in drops, countable motor seizures that do not result in drops, all countable motor seizures, all countable seizures, and all countable seizures that do not result in drops
  - Number of seizure-free days, defined as 1) days with no countable seizures and 2) days with no seizures that result in drops
  - Longest interval between seizures that result in drops
- To evaluate the effect of ZX008 on the following endpoints:
  - Clinical Global Impression – Improvement rating, as assessed by the Principal Investigator.
  - Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver.

2.2.3. Exploratory Objectives

The exploratory objectives of Part 2 are:

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

2.3. STUDY ENDPOINTS

2.3.1. Efficacy Endpoints

The efficacy endpoints for Part 1 of the study are:

Primary Endpoint:

- Percent change from baseline in the frequency of seizures that result in drops in the combined Titration and Maintenance Periods (T+M) in the ZX008 0.8 mg/kg/day group compared to the placebo group.

Key Secondary Endpoints:

- Change from baseline in the frequency of seizures that result in drops 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 Principal Investigator comparing the ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups independently versus placebo.

Additional Secondary Endpoints:
ZX008 0.8 mg/kg/day and 0.2 mg/kg/day groups compared independently versus placebo on the

- 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
- Change from baseline in the frequency of countable seizures that result in drops
- Change from baseline in the frequency of seizures that result in drops between baseline and the Maintenance Period (M)
- Change from baseline in the frequency of countable seizures that do not result in drops
- 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
- 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
- The longest interval (days) between seizures that result in drops 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 parent/caregiver

The efficacy endpoints for Part 2 of the study are:

- The change from baseline in the frequency of seizures that result in drops.

- The change from baseline in the frequency of all countable motor seizures (GTC, TS, CS, AS, TA, FS, MS with a drop)
- The change from baseline in the frequency of all countable seizures
- The 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) from baseline in frequency of all countable seizures that result in drops, countable motor seizures that do not result in drops, all countable motor seizures, all countable seizures, and all countable seizures that do not result in drops
- Number of seizure-free days, defined as 1) days with no countable seizures and 2) days with no seizures that result in drops
- Longest interval between seizures that result in drops
- Clinical Global Impression – Improvement rating, as assessed by the Principal Investigator.
- Clinical Global Impression – Improvement rating, as assessed by the parent/caregiver.

2.3.2. Safety Endpoints

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

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

2.3.3. Exploratory Endpoints

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

- The incidence of medical services used to treat seizures
- The incidence of status epilepticus
- Incidence of rescue medication usage
- Number of days rescue medication used
- The change from baseline in behavior using the Vineland Adaptive Behavior Scale (VABS) (Part 1 only)
- The change from baseline in quality of life using the QOLCE
- The change from baseline in caregiver burden using the Zarit Caregiver Burden Inventory
- The change from baseline in affective symptoms of parent/caregiver using the HADS scale

3. INVESTIGATIONAL PLAN

3.1. OVERALL STUDY DESIGN AND PLAN

This is an international multicenter study being conducted in 2 parts. Up to approximately 80 study sites in North America, Europe, Japan, and Australia are initially 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 only. The primary study endpoint is 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 will consist of a 4-week baseline, 2-week titration, 12-week maintenance, and 2-week taper or transition period. The 4--week Baseline Period will consist 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 will be randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; maximum dose: 30 mg/day) or placebo. Randomization will be stratified by weight (<37.5 kilograms [kg], ≥37.5 kg) to ensure balance across treatment arms, and at least 25% of subjects will be in each weight group. All subjects will be titrated to their blinded randomized dose over a 2-week Titration Period. Following titration, subjects will continue treatment at their randomly assigned dose over a 12-week Maintenance Period. Total treatment time from the beginning of the Titration Period through the end of the Maintenance Period is 14 weeks. 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 will undergo a 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. Safety follow-up visits will be 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 2), as outlined in Table 9.

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, are candidates for continuous treatment for an extended period of time, have met the Selection Criteria for Part 1 (except for criteria related to seizure frequency), and signed informed consent/assent forms prior to the start of Part 2.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. Other requirements for participation in Part 2 are described in Section 4.3. Part 2 will consist of a 12-month Open-Label Extension (OLE) Treatment Period and a 2-week Post-Dosing Period. Thus, subjects who complete Part 2 will have been treated with ZX008 for at least 70 weeks (including their participation in both Part 1 and Part 2). If ZX008 is not commercially available for the treatment of seizures associated with LGS after the end of the OLE Treatment Period, subjects may continue to receive ZX008 in a separate extension protocol. Continuation

will be based on benefit/risk and will be offered to subjects who continue to meet eligibility requirements and comply with Investigator's instructions.

During Part 2 all subjects will be treated initially with 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study subjects. After 1 month at a dose of 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 maximum increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day. 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. See Section 5.5 for instructions on dosing and dose adjustments.

Safety follow-up visits will be performed after study drug discontinuation for early termination and for those subjects who complete Part 2, as outlined in Table 11.

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.

The end of the trial, defined as the last visit of the last subject of Cohort A, is estimated to be the first quarter of 2020 for Part 1 and the first quarter of 2021 for Part 2. A schedule of assessments for Part 1 is provided in Table 1 and for Part 2 in Table 2.

3.2. NUMBER OF SUBJECTS

Approximately 340 subjects will be screened to obtain 250 subjects randomized into Part 1 Cohort A (75 subjects per treatment arm), and at least 30 and up to 50 subjects will be randomized into Part 1 Cohort B. The number of screened subjects may exceed 340 depending on the screen fail rate. Each clinical site will not randomize more than a maximum of 15 subjects without prior consent from the Sponsor.

3.3. STUDY DURATION

The duration of participation in the study for an individual subject is expected to be up to 20 weeks in Part 1 to include:

- Baseline Period – 4 weeks
- T+M Period - 14 weeks
- Taper/Transition Period – 2 weeks after

  Subjects who do not enroll in the open-label extension (Part 2) will undergo a taper off of study medication; eligible subjects who enroll in the open-label extension will undergo a 2-week transition period

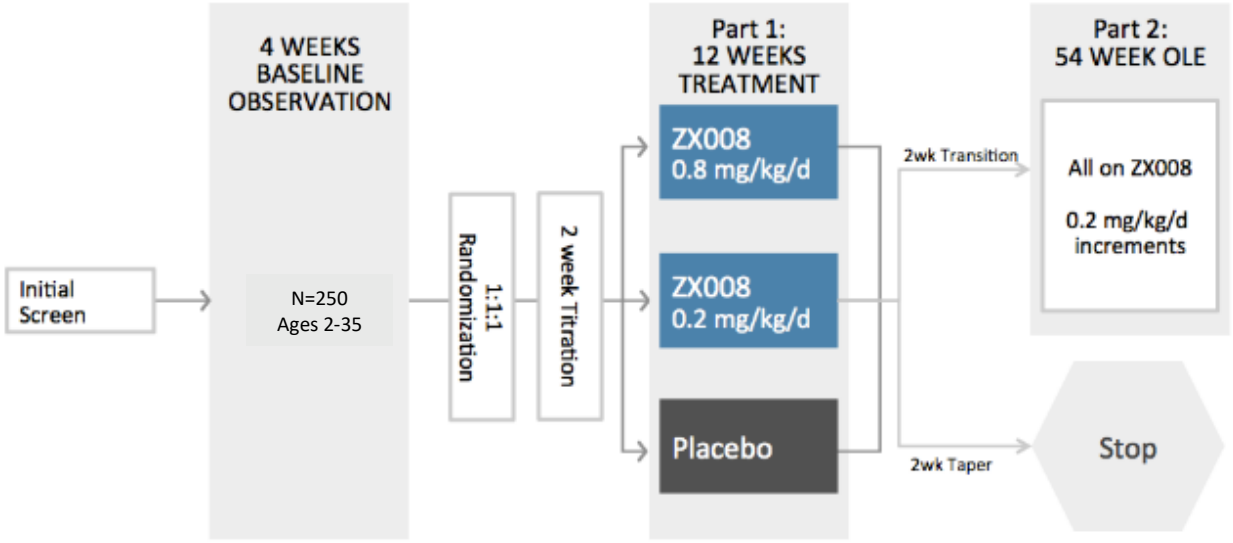
Subjects who enroll in Part 2 will receive ZX008 for up to 54 weeks (which includes a 2-week taper at the end of the open-label extension).

Follow-up cardiovascular safety assessments will be performed following the last dose of study medication for all subjects, regardless of whether they complete the entire study or terminate early. These follow-ups will occur 3 months following the last dose of study medication for any subject taking the medication for 2-13 weeks, and at least 3 and 6 months following the last dose

for any subject taking the medication for >13 weeks. For subjects enrolled in Germany, France and Netherlands, follow-ups will also occur 24 months after the last dose. If there are any findings at a post-dose follow-up, a follow-up visit will be repeated every 3 months until resolved or stabilized.

The study schema is shown in Figure 1.

Figure 1: Study Schema



3.4. NUMBER OF STUDY CENTERS

The study expects to use up to approximately 80 research centers from North America, Europe, Japan, or Australia. Additional study centers within or outside of these geographic areas may be added if enrollment cannot be completed in a timely manner. Sites also may be closed if they fail to enroll.

3.5. RATIONALE FOR STUDY DESIGN AND CHOICE OF TREATMENT GROUPS

It is recognized that performing clinical studies in young children or in subjects with reduced cognitive capacity presents particular practical and ethical issues. However, given the seriousness of LGS, and the possible consequences of current inadequate treatments, the inclusion of children with LGS and adults with LGS who may have intellectual disability in this study is considered justified. Eligible subjects include males and females between 2 and 35 years of age inclusive. Because an accurate diagnosis of LGS is difficult in children younger than 2 years, and seizures that result in drops may not be accurately counted in this age group, children younger than 2 years are not included. Although seizures persist into adulthood, the primary seizure types and the treatment setting may differ, thus adults older than 35 years have not been included in this protocol.

Stratifying the randomization by weight is considered appropriate since the daily dosage of ZX008 increases with weight up to a maximum of 30 mg/day. The two strata in the study will be

subjects who weigh less than 37.5 kg and subjects who weigh 37.5 kg or more. The study design has incorporated a titration period to enable subjects randomized to the high dose group adequate time to acclimate to this dose. Following the Titration Period, subjects will enter a 12-week Maintenance Period where they will continue on their randomized dose for the remainder of the study. The 12-week duration of the Maintenance Period is in keeping with the current standard study duration for evaluating the efficacy of chronic medications. Given the individual variability in seizure frequency and seizure type in this patient population, the primary endpoint, which seeks to compare an appropriate baseline of motor seizure that can result in a drop frequency to the motor seizure that can result in a drop frequency following treatment, is an appropriate primary endpoint for efficacy in this population.

Subjects will receive investigational medicinal product (IMP; ZX008 or placebo) in addition to their existing antiepileptic medications at their stable doses throughout the entire Part 1. Thus, subjects receiving placebo will not be denied active therapy; they will continue to receive their existing medications at the exact same dosages. As the principal study measurement (seizures that result in drops) might be considered subjective, a double-blind study design will prevent subjective bias. Upon completion of Part 1, eligible subjects will be able to receive ZX008 in Part 2, the open-label extension, for up to 1 additional year of treatment.

3.6. RATIONALE FOR COHORT A AND COHORT B

Initial enrollment in Study 1601 was planned at up to 115 study sites in North America, Europe, Australia, and Japan. During the first 14 months of enrollment (ie, between November 2017 and January 2019), 50% of patients were randomized. During the next 5 months of enrollment (ie, between February 2019 and June 2019), enrollment proceeded faster than projected, with the remaining 50% of patients being randomized across a total of 70 active sites.

The speed of enrollment signifies the strong need for new medications for patients with LGS. Amending the Study 1601 protocol to split enrollment into 2 cohorts -- Cohort A (randomized subjects from North America, Europe, and Australia) and Cohort B (randomized subjects from Japan only) -- and pre-specifying the primary analysis endpoint in the protocol and statistical analysis plan to include only subjects from Cohort A allows analyses to be conducted on a suitable number of subjects that are in accordance with the sample size estimations. Moreover, this approach allows evaluation of ZX008 in a Japanese population as part of a global clinical study while adhering to the requirements of the sample size estimation. The number of subjects in Japan will be increased from 15 to at least 30 (with the possibility to include up to 50) in order to provide a suitable sample for comparison, acknowledging that the speed of enrollment in Japan could mimic that of the other countries.

Japan has a large patient population with a high unmet medical need. Cultural differences between Japanese patients and Western patients are well documented in the literature. Moreover, due to operational challenges in clinical trial conduct, patients in Japan are typically not included in global studies, and when they are, it is often in very small numbers proportionally. Analyzing Cohorts A and B independently enables a properly powered primary analysis on Cohort A while providing the opportunity to increase enrollment in Japan in Cohort B, thus allowing for a more substantial comparison of safety and efficacy between Japanese patients and non-Japanese patients.

3.7. PREMATURE TERMINATION OF STUDY

The Sponsor can terminate the study prematurely at any time for medical, ethical, or administrative reasons at individual or at all study sites. The Investigator will be notified in writing, outlining the reasons for the termination. Instructions will be provided if assessments beyond those described in the study protocol need to be conducted.

The Independent Data Safety Monitoring Committee (IDSMC) may request that the study be terminated after review of the safety information at any time during the study.

If the study is terminated prematurely for any reason, the Investigator should promptly inform the subjects participating at his or her study site and should ensure that appropriate follow-up care is available and that End-of-Study procedures are conducted, as described in Section 6.1.2.9 and Section 6.2.4.

All study materials including IMP (unless prior approval for onsite destruction is granted by Sponsor) and completed, partially completed, and blank documentation, except documents needed for archiving requirements, will be returned to the Sponsor. The study monitor will ensure that any outstanding data clarification issues and queries are resolved, and that all study records at the study site are complete.

In accordance with applicable regulatory requirements, the Sponsor will promptly inform the competent regulatory authorities of the termination and its reason(s), and the Investigator or Sponsor will promptly inform the Independent Ethics Committee (IEC)/IRB.

3.8. STUDY MONITORING PROCEDURES

3.8.1. Independent Data Safety Monitoring Committee

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

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

The IDMSC will:

- Be responsible for providing recommendations to the Sponsor surrounding study conduct matters that affect safety. The IDMSC will review the data for the development of heart valve disease and pulmonary hypertension as they occur on a case-by-case basis and at regular meetings.
- Review safety data at ad hoc time points and identify if significant safety concerns arise during the study.
- Review pharmacokinetic data and any other data that may affect subject continuation.

- Make recommendations regarding the continuation, suspension, or termination of the study.

3.8.2. International Cardiac Advisory Board (ICAB)

The ICAB is an advisory body to the Sponsor that assists in monitoring cardiac safety of the ZX008 clinical trials and provides advice to the IDMSC. The ICAB consists of individuals external to the Sponsor who have relevant experience in cardiology, pediatric cardiology, and echocardiography. The ICAB will advise the Sponsor and the IDSMC on the cardiac safety monitoring plan, including alert criteria and decision pathway for subject management relative to cardiac safety in the clinical studies of ZX008 when requested. ICAB members also provide secondary review or adjudication of ECHOs and ECGs, as well as risk assessment, as needed.

4. SELECTION OF STUDY POPULATION

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Before evaluating these criteria and deciding on the eligibility of subjects to participate in the study, it is important that the Investigator is familiar with the safety profile of ZX008 by referring to the Investigator's Brochure, as supplied by the Sponsor. Subjects receiving concomitant STP are not prohibited from study participation. For these subjects the maximum dose will be 0.5 mg/kg/day, with a maximum 20 mg/day, or equivalent placebo volume. For analyses purposes these subjects will be grouped with subjects randomized to 0.8 mg/kg/day. The dose of 0.5 mg/kg/day (maximum 20 mg/day) was selected for concomitant administration with STP based on the predicted effects of concomitant STP on ZX008 and the dose that best matches the exposure for the reference dose (ie, 0.8 mg/kg/day with a maximum of 30 mg/day, in the absence of STP). Both the mg/kg and maximum dose were modified to ensure the best match of exposure in young children (0.5 mg/kg/day) as well as to ensure that individual older patients did not have excursions in exposure (20 mg/day).

4.1. PART 1

4.1.1. Inclusion Criteria

Subjects meeting all of the following inclusion criteria may be enrolled into the study:

1. Subject is male or nonpregnant, nonlactating female, age 2 to 35 years, inclusive as of the day of the Screening Visit. Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative urine or serum pregnancy test at screening. Subjects of childbearing or child-fathering potential must be willing to use medically acceptable forms of birth control (see Section 4.4.2), which includes abstinence, while being treated on this study and for 90 days after the last dose of study drug.
2. Subject must have a diagnosis of Lennox-Gastaut syndrome, where seizures that result in drops are not completely controlled by current antiepileptic treatments. (Subjects without a formal diagnosis may still be enrolled at Sponsor discretion if all other criteria are met.)
3. Subjects must meet all of the following 4 criteria for Lennox-Gastaut syndrome, as defined in this protocol:
    a. Onset of seizures at 11 years of age or younger.
    b. Multiple seizure types (must include TS or TA), including countable motor seizures that result in drops. Countable motor seizure types eligible for inclusion are: GTC, TS, CS, AS, FS with observable motor symptoms, and MS that result in a drop.
    c. Abnormal cognitive development.
    d. Evidence of EEG in the medical history that shows abnormal background activity accompanied by slow spike and wave pattern <2.5 Hz. (Acceptable evidence includes a copy of the EEG trace, EEG report, or physician note that appropriately describes the EEG findings.)
4. Subject must have had at least 8 drop seizures in the last 4 weeks prior to Screening (minimum of 4 drop seizures in the first two weeks and 4 in the last two weeks before baseline), by parent/guardian report to Investigator or investigator medical notes

5. Receiving at least 1 concomitant AED and up to 4 concomitant AEDs, inclusive. The KD and VNS are permitted but do not count towards the total number of AEDs. Rescue medications for seizures are not counted towards the total number of AEDs.
6. All medications or interventions for epilepsy (including KD and VNS) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
7. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
8. Subject has provided assent in accordance with Institutional Review Board (IRB)/Ethics Committee requirements, if capable.
9. Subject's parent/caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.

4.1.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria must not be enrolled into the study:

1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication.
2. Subject's etiology of seizures is a degenerative neurological disease.
3. Subject has a history of hemiclonic seizures in the first year of life.
4. Subject only has drop seizure clusters, where individual seizures cannot be counted reliably.
5. Subject has pulmonary arterial hypertension.
6. Subject has current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke, or clinically significant structural cardiac abnormality, including but not limited to mitral valve prolapse, atrial or ventricular septal defects, patent ductus arteriosus (note: Patent Foramen Ovale or a bicuspid valve are not considered exclusionary).
7. Subject has current or recent history of Anorexia Nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month.
8. Subject has a current or past history of glaucoma.
9. Subject has had an anoxic episode requiring resuscitation within 6 months of the Screening Visit.
10. Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x ULN and/or elevated bilirubin <2x ULN) may be entered into the study after review and approval by the Medical Monitor in conjunction with the Sponsor, in consideration of comorbidities and concomitant medications.
11. Subject has severe renal impairment (estimated glomerular filtration rate <30mL/min/1.73m^2)
12. Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; other centrally-acting noradrenergic agonists, including atomoxetine; or cyproheptadine (see Appendix 1 for a list of prohibited medications).

(Note: Short-term medication requirements for prohibited medications will be handled on a per case basis by the Medical Monitor.)

13. Subject has positive result (as defined in the laboratory manual) on urine or serum tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at the Screening Visit.
14. Subject is taking felbamate for less than 1 year prior to screening and/or does not have stable liver function and hematology laboratory tests, and/or the dose has not been stable for at least 60 days prior to the Screening Visit.
15. Subject is known to be human immunodeficiency virus (HIV) positive.
16. Subject is known to have active viral hepatitis (B or C).
17. Subject is currently receiving an investigational product.
18. Subject has participated in another clinical trial within the past 30 days (calculated from that study's last scheduled visit). Participation in nontreatment trials will be reviewed by the Medical Monitor.
19. Subject is at imminent risk of self-harm or harm to others, in the Investigator's opinion, based on clinical interview and responses provided on the Columbia-Suicide Severity Rating Scale (C-SSRS). Subjects must be excluded if they report suicidal behavior in the past 6 months as measured by the C-SSRS at Screening or Baseline, which includes suicidal ideation with intent and plan (Item #5). If a subject reports suicidal ideation on Item 4 without specific plan, and the Investigator feels that the subject is appropriate for the study considering the potential risks, the Investigator must document appropriateness for inclusion, and discuss with the parent/caregiver to be alert to mood or behavioral changes, especially around times of dose adjustment.
20. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
21. Subject is institutionalized in a general nursing home (ie, in a facility that does not provide skilled epilepsy care).
22. Subject does not have a reliable caregiver who can provide seizure diary information throughout the study.
23. Subject has a clinically significant condition, including chronic obstructive pulmonary disease, interstitial lung disease, or portal hypertension, or has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to the Screening Visit, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.

4.2. RANDOMIZATION INCLUSION CRITERIA

Subjects must meet all of the inclusion criteria and none of the exclusion criteria above and meet the following criteria in order to be randomized:

1. Subject has been approved for study inclusion by the Epilepsy Study Consortium.
2. Subject does not have an exclusionary cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination and is approved for entry by the central cardiac reader. Exclusionary abnormalities include, but are not limited to:
    a. Trace or greater mitral or aortic valve regurgitation in subjects ≤18 years of age
    b. Mild or greater mitral or aortic valve regurgitation in subjects >18 years of age

c. Possible signs of pulmonary hypertension with abnormal or greater than upper range of normal values
d. Evidence of left ventricular dysfunction (systolic or diastolic)

3. Subject demonstrates a stable baseline with ≥ 2 seizures per week resulting in drops during the 4-week Baseline Period.
4. Subject's parent/caregiver has been compliant with diary completion during the Baseline Period, in the opinion of the Investigator and Sponsor.

4.3. PART 2

To be included in Part 2:

1. Subjects must continue to meet the Selection Criteria for Part 1 (except for criteria related to seizure frequency). If a subject entering Part 2 does not meet Randomization Criteria 2 regarding cardiovascular abnormalities, Section 8.9.1 (Follow-up of Cardiovascular Findings) will be applied to determine eligibility to continue into Part 2.
2. All subjects must have satisfactorily completed Part 1 of the study in the opinion of the Investigator and the Sponsor.
3. Review of inclusion and exclusion criteria and written informed parental or guardian consent and assent of minors (if the subject is capable of providing assent) for Part 2 must be obtained before a subject can start any of the Part 2 Visit 15 procedures.
4. Subjects must, in the medical opinion of the Investigator, be candidates for continued treatment for an extended period of time with ZX008. Candidates for continuous treatment should not meet Discontinuation criteria listed in Section 4.5 and should not meet the following criteria:
    a. Clinically meaningful worsening of seizures, judged by Investigator or subject/caregiver such that treatment outside of the protocol and other than ZX008 is assumed to be in the subject's best interest. A clinically meaningful worsening is an increase in frequency, severity or duration of existing seizures, or (in some cases) emergence of a new seizure type. Frequent or increased use of rescue medication may be considered indicative of worsening.
    b. Clinically significant clinical laboratory findings (eg, elevated ALT levels, decrease in platelet count, etc. that are CTCAE Grade 3 or higher) in subjects with no prior relevant history, that were not present during Baseline, are confirmed by a repeat test within a week, and not attributable to other concomitant medications.
    c. Weight loss >15% during the T+M period that has not stabilized and is considered, in the opinion of the Investigator, detrimental to continuing treatment with ZX008.
5. Those subjects who do not complete the 12-week Maintenance Period of Part 1 may, on a case-by-case basis, be eligible for entrance after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a ZX008 trial. The decision whether to permit participation in Part 2 for subjects who do not complete Part 1 resides solely with the Sponsor, who will require a formal request for early Part 2 continuation to be made by the Investigator as well as an evaluation of

risk/benefit. The Sponsor may consult with the site Investigator, the ICAB and/or the IDSMC, and take into consideration evidence of the following for approval:

a. The subject is experiencing a worsening in condition that is not likely to be related to Part 1 treatment, in the opinion of the Investigator
b. The subject has progressed at least half-way through Part 1 (ie, Visit 8)
c. The subject has been compliant with assessments and requirements of Part 1
d. The subject does not exhibit other contraindications to initiating open-label treatment

4.4. SUBJECTS OF REPRODUCTIVE POTENTIAL

Male subjects who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of highly effective contraception from the time of informed consent until 90 days after the last dose of study drug.

The following methods are acceptable:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable intrauterine device
    - intrauterine hormone-releasing system
- Surgical sterilization (vasectomy or bilateral tubal occlusion)

Female subjects who are not of childbearing potential do not need to use any methods of contraception. A woman is considered of childbearing potential, unless they are at least 2 years post-menopausal or permanently sterile, or if she has not yet reached menarche. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Female subjects who are sexually active and are of childbearing potential must use, with their partner, an approved method of highly effective contraception from the time of informed consent until 90 days after the last dose of study drug.

The following methods are acceptable:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation and a barrier method (ie, condom for male partner):
    - oral
    - intravaginal
    - transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation and a barrier method (ie, condom for male partner):
    - oral
    - injectable
    - implantable intrauterine device
    - intrauterine hormone-releasing system
- Surgical sterilization (vasectomy or bilateral tubal occlusion)

Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they, with their partner, they must comply with the contraceptive requirements detailed above.

4.4.1. Sperm and Egg Donation

Male subjects should not donate sperm and female subjects should refrain from egg donation for the duration of the study and for at least 90 days after the last day of study medication administration.

4.4.2. Pregnancy

Subjects will be instructed that if they/their partner become pregnant during the study this should be reported to the Investigator. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject/subject's partner is subsequently found to be pregnant after the volunteer is included in the study, then consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery. Any subject reporting a pregnancy during the study will be withdrawn from the study drug by completing the taper schedule. All safety follow-up activities must be completed.

4.5. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

While subjects are encouraged to complete all study evaluations, subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they fail to return for visits or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the Investigator must make a genuine effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the electronic case report form (eCRF). All subjects who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. If a subject withdraws prematurely after dosing, all data to be collected prior to discharge from the clinical site should be collected at the time of premature discontinuation or at the scheduled discharge.

For subjects who are lost to follow-up (ie, those subjects whose status is unclear because they failed to appear for study visits without stating an intention to withdraw), the Investigator should show "due diligence" by documenting in the source documents the steps taken to contact the subject (eg, dates of telephone calls, registered letters).

Subjects must be discontinued from the study for the following reasons, if deemed appropriate by the sponsor or investigator:

1. Development of signs or symptoms indicative of cardiac valvulopathy or regurgitation (mitral, aortic, tricuspid, pulmonary valves), or pulmonary hypertension for which IDSMC, in consultation with cardiac readers and the Investigator believe the benefit of continued participation does not outweigh the risk.
2. Subject is found to have entered the clinical investigation in violation of the protocol.
3. Subject requires or starts using unacceptable or contraindicated concomitant medications, or currently utilized chronic daily seizure therapy is changed.
4. Subject's condition changes after entering the clinical investigation so that the subject no longer meets the inclusion criteria or develops any of the exclusion criteria.
5. Subject is noncompliant with procedures set forth in the protocol in an ongoing or repeated manner.
6. Subject experiences an AE that warrants withdrawal from the clinical investigation.
7. Clinically significant worsening of seizures, judged by Investigator or subject/caregiver such that treatment outside of the protocol and other than ZX008 is assumed to be in the subject's best interest. Frequent or increased use of rescue medication may be considered indicative of worsening.
8. An "actual suicide attempt" as classified by the Columbia-Suicide Severity Rating Scale (C-SSRS).
9. It is the Investigator's opinion that it is not in the subject's best interest to continue in the study.
10. Subject is found to be pregnant while on study. Subject will be withdrawn following the taper schedule; all safety follow-up activities must be completed.

Discontinuation decisions will be made at each participating site by the site Investigator. Discontinuations due to development of cardiovascular or cardiopulmonary complications are to be made by the IDMSC.

If feasible, the process of discontinuation should be discussed with the Medical Monitor. The decisions regarding the discontinuation of the investigational therapy, whether the study medication should be stopped immediately or tapered should be discussed with the Medical Monitor, but final decisions about the process will remain at the discretion of the site Principal Investigator.

Subjects who are discontinued from the clinical investigation for any reason will not be replaced.

Subjects may withdraw their consent to participate in the study at any time without having to justify the reason for doing so. The decision to withdraw consent and discontinue participation in the study will not prejudice the subject's future medical treatment in any way.

Subjects must be discontinued from receiving ZX008 and/or participating in any further study procedures under the following circumstances:

- The subject or the subject's legally authorized representative wishes to discontinue participation in the study.

- The Investigator advises that the subject's safety or well-being could be compromised by further participation in the study.
- The Sponsor requests that a subject discontinues participation in the study (eg, due to suspicion of fraud, multiple enrollments in clinical studies, lack of compliance).

In the event that the study is terminated prematurely then the procedure for termination should be followed as described in Section 3.7. Concern for the interests of the subject will always prevail over the interests of the study.

The reason for, and date of discontinuation from participation in the study must be recorded in detail in the eCRF and in the subject's medical records (eg, AEs, lack of compliance, lost to follow-up, etc.). If possible, the subject/subject's legally authorized representative should confirm his decision in writing.

The Investigator will attempt to complete all procedures usually required at the end of the study at the time when the subject's participation in the study is discontinued or as close as possible to that time. Specific procedures required for each Part of the study are described in Section 6.1.2.9 and Section 6.2.4. As far as possible, a complete final examination must be performed on all subjects who do not complete the study according to the study protocol.

Data collected until the time a subject discontinues participation in the study will be handled in the same manner as data for subjects completing the study. Where possible, further information will be collected if any AEs are experienced by a subject after discontinuing participation in the study.

4.6. TERMINATION OF THE CLINICAL STUDY

If the Investigator, the Sponsor, the Medical Monitor, or the IDSMC becomes aware of conditions or events that suggest a possible hazard to subjects if the clinical study continues, then the clinical study may be terminated. The decision to terminate the study is solely with the Sponsor. The clinical study may be terminated at the Sponsor's discretion at any time also in the absence of such a finding.

Conditions that may warrant termination of the clinical study include, but are not limited to:

- The discovery of an unexpected, relevant, or unacceptable risk to the subjects enrolled in the clinical study.
- Failure to enroll subjects at the required rate.
- A decision of the Sponsor to suspend or discontinue development of ZX008.

4.7. REPLACEMENT OF SUBJECTS

Enough subjects will be enrolled in Part 1 of the trial to ensure that approximately 250 subjects are randomized into the T+M period of Part 1 Cohort A, and at least 30 and up to 50 subjects are randomized into Part 1 Cohort B. Randomized subjects will not be replaced.

5. INVESTIGATIONAL MEDICINAL PRODUCT INFORMATION

ZX008/matching placebo will be administered in the current study. A brief description of the ZX008 product is provided below (Table 3).

Table 3: Investigational Medicinal Product – ZX008

	Study Product
Substance Code	ZX008
Active Substance (INN)	Fenfluramine Hydrochloride
Trade Name	Not applicable
Formulation (including dosage form and strength)	Solution 1.25, 2.5, and 5 mg/mL
Route/Mode of Administration	Oral
Manufacturer	PCI Pharma Services on behalf of Zogenix International Limited

5.1. IDENTITY OF INVESTIGATIONAL MEDICINAL PRODUCT

ZX008 drug product is an oral aqueous solution of fenfluramine hydrochloride buffered to pH 5 and provided in concentrations of 1.25 mg/mL, 2.5 mg/mL, and 5 mg/mL. The excipients selected have been approved for use in the formulations of currently marketed drug products and are considered to be safe. The solution formulations will be suitably flavored, and will contain preservatives and a thickening agent. The product is sugar free and is intended to be compatible with a KD.

The formulation for Part 1 will be provided in bottles with tamper-evident, child-resistant caps. The clinical trials material will be supplied in 1 bottle size with nominal fill volume of 120 mL. Matching placebo also will be provided. Doses to be studied include ZX008 0.2 mg/kg/day and ZX008 0.8 mg/kg/day divided into two daily (BID) doses, up to a maximum of 30 mg/day (subjects taking concomitant STP will receive 0.5 mg/kg/day, up to a maximum of 20 mg/day, or equivalent volume of placebo). An intermediate dose of 0.4 mg/kg/day will be used for titration. The concentration of ZX008 oral solution received by subjects (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) will be randomized across the 3 available concentrations in order to ensure blinding.

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

5.1.1. Labeling and Packaging

The ZX008 product will be packaged and labeled according to current International Conference on Harmonization (ICH), Good Manufacturing Practices (GMP), and Good Clinical Practices (GCP) guidelines, and national legal requirements.

Dosing directions for the product can be found in the Pharmacy Manual for the study subjects and for the Investigator.

5.2. DESCRIPTION OF REFERENCE TREATMENT, COMPARATOR, AND/OR PLACEBO

Placebo solution is identical in aspect and composition to ZX008 and is composed of identical ingredients used in the ZX008 formulation, except that it does not contain the active ingredient, fenfluramine hydrochloride. Subjects randomized to placebo will receive concentration equivalent volumes of investigational product that does not include the active ingredient.

No comparators or reference treatments will be used.

5.2.1. Labeling and Packaging

Placebo solution will be packaged in an identical manner to ZX008. The matching placebo product will be packaged and labeled according to current ICH, GMP, and GCP guidelines, and national legal requirements.

Dosing directions for the product can be found in the IMP handling instructions for the study subjects and for the Investigator.

5.3. SHIPMENT AND STORAGE

IMP will be supplied to the study sites by the Sponsor or its delegate.

All IMP will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions supplied to the research site and its designated pharmacy, the site's standard operating procedures, and applicable regulations. IMP must be stored separately from normal hospital or practice inventories, in a locked facility with access limited to the Investigator and authorized personnel. The Investigator must ensure that the IMP is dispensed only to subjects enrolled in this study according to this study protocol.

Appropriate storage temperature and transportation conditions will be maintained for the study drug from the point of manufacture up to delivery of the study drug. Study medication must be stored at 15 to 25°C (59 to 77°F) with excursions of 5 to 40°C (41 to 104°F) permitted; do not refrigerate or freeze.

Storage and handling instructions of the IMP maintained at the subject's home are described in the subject's IMP handling instructions.

All unused IMP will be saved by the site for final disposition according to the Sponsor's directive.

5.4. IMP ACCOUNTABILITY

The Investigator or delegate will confirm receipt of all shipments of the IMP in writing using the receipt form(s) provided by the Sponsor or vendor.

Assignment of ZX008 or placebo to the subject will be handled through an Interactive Web Response (IWR) platform. The Investigator or delegate will be required to register the subject through IWR and all study medication will be assigned to the subject through the IWR. The IWR will also maintain a log of all received and dispensed medication.

All supplies must be accounted for throughout the study using the drug accountability form provided by the Sponsor before the start of the study. Drug accountability is the process of documenting all aspects of drug receipt, storage, use, and disposition so that a full accounting of each unit can be made. This includes administration, and return and/or destruction of study drug. At the end of the study, the dated and signed (by the Investigator or delegate, eg, pharmacist) original drug accountability form must be retained at the study site as verification of final drug accountability.

Records for the delivery of the IMP to the study site, the inventory at the study site, the use by each subject (use by subject will be documented in the subject diary), and the destruction or return of the IMP to the Sponsor must be maintained by the Investigator (or delegate). The records will include dates, quantities, batch numbers, and unique code numbers assigned to the IMP and to the subjects. The Investigator must maintain records documenting that subjects were provided with the doses of the IMP specified in this study protocol. Furthermore, the Investigator must reconcile all IMPs received from the Sponsor. The Investigator must provide reasons for any discrepancies in drug accountability. Forms will be provided by the Sponsor to ensure standardized and complete drug accountability.

5.5. TREATMENT ADMINISTRATION

5.5.1. Part 1: Randomization

Upon completion of the Baseline period in Part 1, subjects who qualify for the study will be randomized (1:1:1) in a double-blind manner to receive 1 of 2 doses of ZX008 (0.2 mg/kg/day, 0.8 mg/kg/day; 30mg/day maximum [0.5 mg/kg/day; 20 mg/day maximum for subjects taking concomitant STP]) or placebo. The randomization will be 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 will be assigned a randomization number by the IWR system upon confirmation that subject qualifies for enrollment in the Titration period. Once a randomization number is assigned to a subject, the site will record the subject's initials and identification number on the corresponding study drug bottles. Each bottle will contain the 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 will be identical, thus rendering the study drug and placebo indistinguishable. For each IMP bottle and randomization number assigned, the following information will be recorded on the drug accountability form: subject initials, unique bottle number, date each bottle is assigned, and drug used and unused during the study.

5.5.1.1. Blinding

The blinding scheme instituted for this study will ensure that the volume of study medication taken cannot be associated with the dose group, thus unblinding the study. This is achieved by random assignment of different concentrations of the ZX008 oral solution (1.25 mg/mL, 2.5 mg/mL, and/or 5 mg/mL) by the IWR system. The IWR system will instruct site personnel to the volume of oral solution to be administered based on that subject's weight. (Dose will be recalculated by the system based on weight once at the midpoint of the study.) During the Titration, Maintenance, and Taper/Transition periods, the subjects and study personnel

(Investigators, clinical staff, personnel involved in data collection and analysis, the Medical Monitor, and the Sponsor) will be blinded to the treatment allocation and to the concentration of ZX008 oral solution. If an Investigator feels the blind should be broken, he/she can do so when necessary for treatment decisions. However, the Investigator should endeavor to discuss with the Medical Monitor or Sponsor's Medical Representative, if available. The blind should only be broken in the event the knowledge of whether the subject is on active study medication versus placebo is needed to determine course of medical treatment for the event. The subject will be discontinued from the clinical trial upon breaking of the blind and the decision whether the subject can enter Part 2 will rest with the Sponsor if the subject exited Part 1 prior to completion.

5.5.2. Part 1: Titration Period

The Investigator (or delegate) will dispense IMP only to subjects included in Part 1 of this study following the procedures set out in this study protocol.

Study medication will be administered as equal doses BID in the morning and in the evening approximately 12 hours apart. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given.

If the parent/caregiver is unable to administer the full dose due to spillage (eg, dose was spilled during measuring, subject spit dose out during administration), he/she should attempt to give the full dose noting the extra amount used to fulfill the dose. If the subject vomits within the first 15 minutes of administration the dose may be readministered. **Care must be taken not to overdose.** If the amount spilled is not known, the parent/caregiver should not give additional medication to avoid potential overdose.

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

In order to maintain the blind across all dose groups in Part 1 (Section 5.5.1.1) and allow step titration to the high dose, the dose for each subject will be titrated starting with a dose of ZX008 0.2 mg/kg/day (or placebo equivalent) BID. After 4 days at this dose level (Study Day 5), subjects randomized to the ZX008 0.8 mg/kg/day (or 0.5 mg/kg/day for subjects taking concomitant STP) group will increase their dose to 0.4 mg/kg/day (maximum 30 mg/day or 20 mg/day for subjects taking concomitant STP) while doses in the other two groups will remain constant. On Study Day 9, the dose for the 0.8 mg/kg/day group (or 0.5 mg/kg/day for subjects taking concomitant STP) will increase to the target dose or a maximum of 30 mg/day (or 20 mg/day for subjects taking concomitant STP). The titration is expected to take a total of 14 days (Table 4). A new bottle of IMP will be started by the subject at each level of the titration step. See Section 5.1 for more information about the volume of ZX008 or placebo to be administered. If a subject does not tolerate IMP during titration, slower titration may be considered after consultation with the Medical Monitor.

Table 4: Titration Algorithm for Part 1

Randomized Group	Titration Step 1 Study Day 1-4	Titration Step 2 Study Days 5-8	Titration Step 3 Study Days 9-14
ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day (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
Note: maximum daily dose of ZX008 is 30 mg (20mg for subjects taking concomitant STP)			

5.5.3. Part 1: Maintenance Period

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

5.5.4. Part 1: Taper Period (for subjects not entering Part 2)

Subjects who complete the Maintenance period and will not be continuing into Part 2, the open-label extension, and subjects who discontinue from Part 1 early, will be tapered off of study medication. Study medication will be administered as equal doses BID in the morning and in the evening approximately 12 hours apart. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given. IMP should be administered using the oral dosing syringe provided.

If the parent/caregiver is unable to administer the full dose due to spillage (eg, dose was spilled during measuring, subject spit dose out during administration), he/she should attempt to give the full dose noting the extra amount used to fulfill the dose. If the subject vomits within the first 15 minutes of administration the dose may be readministered. **Care must be taken not to overdose.** If the amount spilled is not known, the parent/caregiver should not give additional medication to avoid potential overdose.

In order to maintain the blind across all dose groups, all subjects who do not continue into Part 2 will participate in a blinded dose-tapering procedure over the course of 8 days. On the first day of the tapering period subjects in the ZX008 0.8 mg/kg/day group (or 0.5 mg/kg/day for subjects taking concomitant STP) will decrease to a dose of ZX008 0.4 mg/kg/day BID (maximum 30 mg/day or 20 mg/day for subjects taking concomitant STP). After 4 days at this dose level (Study Day 5), subjects in this group will decrease their dose to 0.2 mg/kg/day. Subjects in the ZX008 0.2 mg/kg/day group will decrease their dose to placebo on the first day of tapering while doses in the placebo group will remain constant throughout the tapering procedure. On Study Day 9, all subjects will stop taking study medication. The taper is expected to take a total of

8 days (Table 5). A new bottle of IMP will be started by the subject at each level of the taper step.

Table 5: 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

Note: maximum daily dose of ZX008 is 30 mg (20 mg for subjects taking concomitant STP).

5.5.5. Part 1: Transition Period

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 (Table 6).

All subjects entering the open-label extension (Part 2) will be transitioned from their blinded daily dose to the 0.2 mg/kg dose during the 2-week interval between Visits 12 and 15, without breaking the blind. The IWR system will assign two bottles of IMP to the subject, one for each step in the transition. A new bottle of IMP will be started by the subject at each level of the transition step. See Section 5.1 for more information about the volume of ZX008 or placebo to be administered.

Table 6: Transition Algorithm for Part 1

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

Note: maximum daily dose of ZX008 is 30 mg (or 20 mg for subjects taking concomitant STP).

Subjects who had been randomized to placebo increase their dose to 0.2 mg/kg/day beginning on Day 1 of the transition (the day following Visit 12). Subjects who had been randomized to 0.2 mg/kg/day will continue to receive that dose. Subjects who had been randomized to 0.8 mg/kg/day or were receiving the maximum dose of 30 mg/day (or subjects taking concomitant STP and randomized to 0.5 mg/kg/day; 20 mg/day maximum) decrease to a dose of ZX008 0.4 mg/kg/day, or a maximum of 30 mg/day (20 mg/day for subjects taking concomitant STP). After 4 days at this dose level (Day 5), these subjects will decrease their dose to 0.2 mg/kg/day. Subjects will report to the clinic on Day 14 for enrollment into the open-label extension.

Study medication will be administered as equal doses BID in the morning and in the evening approximately 12 hours apart. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given. Study medication should be administered using the oral dosing syringe provided.

If the parent/caregiver is unable to administer the full dose due to spillage (eg, dose was spilled during measuring, subject spit dose out during administration), he/she should attempt to give the full dose noting the extra amount used to fulfill the dose. If the subject vomits within the first 15 minutes of administration the dose may be readministered. Care must be taken not to overdose. If the amount spilled is not known, the parent/caregiver should not give additional medication to avoid potential overdose.

5.5.6. Part 2: OLE Treatment Period

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

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

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

If after approximately the midway point of the first 30 days on ZX008 0.2 mg/kg/day there is a clinically meaningful worsening in seizure type, frequency, and/or duration compared with the recent treatment in the core study, the Investigator, in consultation with the Medical Monitor and approval of the Sponsor, may increase the dose to 0.4 mg/kg/day (maximum 30 mg/day or 20 mg/day for subjects taking concomitant STP). A clinically meaningful worsening would be an increase in frequency, severity or duration of existing seizures, or (in some cases) emergence of a new seizure type. The description of clinical worsening must be documented in the source notes and case report form (CRF). Further increase to 0.8 mg/kg/day (maximum 30 mg/day or 0.5 mg/kg/day; maximum 20 mg/day for subjects taking concomitant STP) could also be undertaken for the same conditions after a minimum of 4 days on 0.4 mg/kg/day, if the condition has not stabilized on the 0.4 mg/kg/day dose. Dosing outside of the specified range (ie, up to 0.8 mg/kg/day [or 0.5 mg/kg/day for subjects taking concomitant STP]) may be considered after consultation between the Investigator and Medical Monitor and approval of the Sponsor;

however, excursions over 30 mg/day (or 20 mg/day for subjects taking concomitant STP) are prohibited.

Study medication will be administered as equal doses BID in the morning and in the evening, approximately 12 hours apart. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given.

If the parent/caregiver is unable to administer the full dose due to spillage (eg, dose was spilled during measuring, subject spit dose out during administration), he/she should attempt to give the full dose noting the extra amount used to fulfill the dose. If the subject vomits within the first 15 minutes of administration the dose may be readministered. Care must be taken not to overdose. If the amount spilled is not known, the parent/caregiver should not give additional medication to avoid potential overdose.

5.5.7. Taper Period

All subjects (those who complete the Part 2 OLE Treatment period and those who discontinue from the study early) will be tapered off of study medication.

The tapering scheme is a 2-step process as described in Table 7.

Study medication will be administered as equal doses BID in the morning and in the evening, approximately 12 hours apart. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given. IMP will be administered using the oral dosing syringe provided.

Table 7. Taper Algorithm for Part 2

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

Note: maximum daily dose of ZX008 is 30 mg (or 20 mg for subjects taking concomitant STP).

5.6. PRIOR AND CONCOMITANT MEDICATION

All medications taken by a subject before receiving study medication (ie, during the Screening and Baseline Seizure Assessment periods in Part 1) and stopped before the first administration of IMP are regarded as prior therapy and must be documented in the eCRF. Significant medications (eg, antibiotics) taken within 30 days prior to the Screening visit should also be captured. All prior and concomitant AEDs will be collected in the eCRF.

All medications taken by a subject after the first administration of IMP, including those that started before the first administration of IMP and are continuing, are regarded as concomitant medication and must be documented in the eCRF, including over-the-counter medication, herbal and vitamin/supplement preparations.

Subjects are required to take at least one concomitant AED during study participation. No new concomitant AEDs may be introduced while in this study without discussion with the Medical Monitor prior to initiation. Nonstudy medications and therapies (this does not include KD, VNS, and RNS) that are considered necessary for the subject's welfare and will not interfere with the response to the study medication may be given at the discretion of the Investigator, informing the Medical Monitor as soon as possible.

It should be noted for any subject receiving hypoglycemic agents, the Investigator should consider diabetic medication changes in the setting of weight loss and hypoglycemia.

Part 1

All subjects will continue to receive their existing AED(s) with the same doses throughout the Part 1 Double-blind Treatment period. Every effort should be made to ensure that the regimen of existing medications remains stable during Part 1; any changes must be discussed with the Sponsor prior to implementation. If a decrease in a concomitant AED is necessary to manage an AE, this must be discussed with the Sponsor as soon as possible after implementation if not before implementation. Increases in dose or number of concomitant AEDs are not permitted during Part 1 of the study.

Part 2

During at least the first 6 months of the Part 2 OLE Treatment period, subjects will continue to receive their existing AEDs at the same dose and frequency as prior to starting Part 2. However, once the subject has been stable on a ZX008 dose for at least 6 months with good seizure control, Investigators will be allowed as per typical clinical practice to alter one or more other concomitant AED doses as deemed clinically appropriate. Subjects who achieve robust seizure control may be considered to decrease concomitant AEDs earlier than 6 months after review/ discussion with the Medical Monitor and approval from the Sponsor. Concomitant AEDs may be withdrawn completely but all subjects must remain on a minimum of 1 concomitant AED plus ZX008. Addition of new concomitant AEDs must be discussed with and approved by the Medical Monitor prior to initiation. All medication dose changes must be documented with a clinical explanation and justification. Concomitant AED dose adjustments outside of these parameters should be discussed with the Medical Monitor prior to initiation.

5.6.1. Vagal Nerve Stimulation

Subjects receiving treatment with a VNS may be included as long as the VNS has been in place for at least 6 months prior to entry into the study, the VNS battery is not due for replacement during the study, and stimulation parameters have been kept constant for 4 weeks prior to screening and must remain so throughout the study. VNS may not be the only anti-epileptic treatment (ie, it does not count as an AED but it does count as a treatment for LGS). The subject's use of VNS will be recorded in the eCRF.

During at least the first 6 months of the Part 2 OLE Treatment period, VNS stimulation parameters will be kept constant. However, once the subject has been stable on a ZX008 dose for at least 6 months with good seizure control, Investigators will be allowed as per typical clinical practice to alter VNS stimulation parameters as deemed clinically appropriate. All VNS stimulation parameter changes must be documented with a clinical explanation and justification. VNS stimulation parameter adjustments outside of these boundaries should be discussed with the Medical Monitor prior to initiation.

5.6.2. Ketogenic Diet

Adherence to the KD, or a modified version of KD, is permitted during the study if the dietary habits were initiated more than 4 weeks prior to Screening and remain stable throughout the study. KD may not be the only anti-epileptic treatment (ie, it does not count as an AED but does count as a treatment for LGS). The subject's use of KD will be recorded in the eCRF.

During at least the first 6 months of the Part 2 OLE Treatment period, the KD will be adhered to. However, once the subject has been stable on a ZX008 dose for at least 6 months with good seizure control, Investigators will be allowed as per typical clinical practice to alter the KD as deemed clinically appropriate. All KD changes must be documented with a clinical explanation and justification. KD adjustments outside of these parameters should be discussed with the Medical Monitor prior to initiation.

5.6.3. Rescue Medication for Seizures

The subject's usual or prescribed regimen and frequency of rescue therapy for seizures should be entered into the concomitant medication sections of the eCRF and identified as a rescue medication by selecting the appropriate box.

Use of rescue medication is permitted during the study and should be recorded on the eCRF (day, medication[s], dose[s]) and in the diary (day, timeframe associated with seizure episodes). Repeated administrations within the same episode should be recorded separately.

5.6.4. Prohibited Concomitant Medications

Examples of concomitant medications in the classes prohibited are listed in Appendix 1 and summarized below. If medical necessity requires short-term use of one or more of these medications during the course of the study, please contact the Medical Monitor for approval.

- Felbamate is prohibited as a concomitant medication unless the subject has been on felbamate for at least 12 months prior to screening, has stable liver function and

hematology laboratory tests, and the dose has been stable for at least 60 days prior to screening and is expected to remain constant throughout the study.

- Products that contain cannabis and/or cannabinoids are prohibited for the duration of participation in the study.
- Drugs that interact with central serotonin: imipramine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, vortioxetine.
- Drugs that increase cardiovascular risk: eg, atomoxetine.
- Drugs intended to facilitate weight loss.
- Ergot alkaloids and their derivatives, including pergolide and cabergoline
- Phenylpropanolamine and other decongestants may be used for short-term use only.

5.7. TREATMENT COMPLIANCE

Each subject or parent/caregiver will record the dose, dosing frequency and IMP consumption in the subject's diary. Subjects will bring their used, partially used, and unused IMP to every study visit. Treatment compliance will be monitored by measuring the volume of IMP in these bottles and comparing to the dispensation log and diary records.

6. VISIT SCHEDULE

6.1. PART 1

Study procedures for the Part 1 Double-blind Treatment period will be conducted according to the Schedule of Assessments in Table 1. Time windows for all assessments in Part 1 are detailed in Table 8.

Table 8: Time Windows for Assessments in Part 1

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Clinic; Study Day -29 to -28 or -28 to -27): Screening)	Not applicable
Visit 2 (Phone; Study Day -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
Blood collection for ZX008 PK	± 15 minutes

Abbreviations: AED=antiepileptic drug (s); ECHO=echocardiogram; PK = pharmacokinetics

[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] Depending on country requirements. See Table 9 for details.

6.1.1. Baseline Period (Study Day -28 to Study Day -1)

The Baseline period of the study encompasses the screening activities that will occur on Study Day -28 as well as the observation period where subjects will be assessed for baseline seizure activity based on recordings of daily seizure activity entered into a diary.

6.1.1.1. Screening, Clinic Visit 1 (Study Day -28)

Screening is the predetermined series of procedures with which each Investigator selects an appropriate and representative sample of subjects for enrollment into the study. Select screening data will be documented in the IWR and eCRF.

Written informed parental or guardian consent and assent of minors (if the subject is capable of providing assent) must be obtained before a subject can start any of the screening procedures. The procedure(s) for obtaining written informed consent and assent of minor (if the subject is capable of providing assent) are described in Section 11.2.

The Screening visit will occur on Study Day -28; however, the procedures may be split over 2 consecutive days (eg, Study Day -29 and Study Day -28 or Study Day -28 and Study Day -27). Splitting the visit procedures across 2 nonsequential days requires the approval of the medical

monitor. The following procedures will be performed for all subjects before the start of seizure activity observation:

- Obtain written informed consent for the study
- Obtain written informed consent from parent/caregiver to collect information about parent/caregiver symptoms and burden via the Zarit Caregiver Burden, and HADS rating
- Review inclusion and exclusion criteria
- Review retrospective seizure diary data
- Record demographic information
- Record medical, neurological, and epilepsy history
- Record current epilepsy status (number/type/duration seizures per month); submit form to Epilepsy Study Consortium
- Collect past 6 months (or available duration) of parent/caregiver seizure diary data if available (screen shots of cell phones are acceptable, as are photocopies of paper diaries or print outs) and place in source file
- Record prior medications
- Complete physical examination, including height and weight
- Complete neurological examination
- 12-lead electrocardiogram
- Doppler ECHO (this may be obtained any time between Study Day -28 and Study Day -15)
- Vital signs
- Urine or serum pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, hematology, immunoglobulin, and urinalysis)
- Urine or serum THC panel
- Whole blood CBD
- C-SSRS Baseline/Screening Assessment (Appendix 2)
- Instruct parent/caregiver on use of diary
- Dispense diary (after above procedures have been concluded; the 28-day period for determining baseline seizure frequency begins when screening assessments are completed and the seizure diary is dispensed)
- Record AEs
- Record AESIs

Only eligible subjects as specified by the inclusion and exclusion criteria who are independently confirmed to be eligible by the Epilepsy Study Consortium will be enrolled into the study.

After enrollment into the study, each subject will be issued a "Subject Card" containing information about the subject's participation in the study. The subject or parent/caregiver will be advised to retain this card on his person for the entire duration of the study so that the Investigator or the Sponsor can be contacted in case of emergency.

In certain circumstances the Sponsor may allow subjects who did not meet all inclusion/exclusion criteria at the time of the Screening Visit to have the screening period extended, or to be re-screened for eligibility. In all cases the Investigator should consult with the Medical Monitor. Decisions whether to permit rescreening resides solely with the Sponsor.

The decision whether to permit extended screening or rescreening can be influenced by many factors individual to that subject case. Some general principles apply:

1. If baseline seizure screening is extended or the subject is discontinued and then rescreened, the screening period for establishing the baseline seizure frequency will be the immediate 4 weeks before the randomization visit.
2. Subjects who are found to be on a prohibited medication at the screening visit may be weaned off of that medication provided:
    a. Decisions to withdraw a disallowed concomitant medication must be made with the agreement of the prescribing physician
    b. If the medication has antiepileptic properties, a wash out of at least 5 half-lives must be completed before collection of baseline seizure data.
    c. If a decision has been made to wean off of a medication without antiepileptic properties and the washout period (at least 5 half-lives) is expected to be shorter than 3 weeks, then the subject may remain in screening and chart seizures using the seizure diary.
3. If screening is extended, laboratory and ECHO assessments must be at least 6 weeks current at the time of Randomization. Assessments older than 6 weeks will need to be repeated prior to Randomization. If laboratory assessments are repeated within 2 weeks of Randomization, samples do not need to be collected during Visit 3, provided valid results are obtained.

6.1.1.2. Phone Visit 2 (Study Day -15)

Site personnel will contact the subject via telephone on Study Day -15 and record the following:

- AEs
- AESI

In addition, site personnel will review the diary entries with the parent/caregiver. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.

6.1.1.3. Clinic Visit 3 (Study Day -1): Randomization

This period is intended to ensure that subjects meet the study entry criteria and confirm they have experienced ≥ 2 seizures resulting in drops per week during the 4-week Baseline period. Subjects must have at least 28 days of prospective diary data at Visit 3.

The following procedures will be performed on Study Day -1:

- Review inclusion and exclusion criteria
- Review current seizure activity (number/type/duration) from diary since previous visit and calculate the number of seizures resulting in drops per week and over the 4-week observation period.
- Ensure approval for enrollment has granted by the Epilepsy Study Consortium and after ECHO review (ERT).
- Record prior medications since previous visit
- Complete physical examination, including weight
- Abbreviated neurological examination
- Vital signs
- 12-lead ECG
- For subjects enrolled in France or Netherlands only: conduct a chest x-ray
- Urine or serum pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, hematology, immunoglobulin, hormones, coagulation, and urinalysis (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)
- Collect plasma sample for AED pharmacokinetic evaluation (must document time of last dose)
- Urine or serum THC panel
- Whole blood CBD
- Obtain (optional) blood sample for epilepsy genotype panel (if not obtained at this visit, it should be obtained by Visit 12)
- Tanner Staging for subjects >7 to 18 years of age (Appendix 5)
- Collect, review, and dispense diary. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.
- C-SSRS Since Last Visit Assessment (Appendix 2)
- BRIEF (Appendix 3)
- QOLCE (Appendix 6)
- HADS (Appendix 7)
- Zarit Caregiver Burden Inventory (Appendix 8)
- Record AEs
- Record AESI
- When eligibility for the Titration period is confirmed, obtain treatment assignment from the IWR

- Dispense study medication
  (If administration of the first dose of study medication occurs in the clinic, this dose will be recorded in the eCRF, but not the subject diary, and the next dose should be at least 8 hours later or the following morning. The dose on the following morning will count as Study Day 1 and be recorded in the subject diary.)

6.1.2. Titration and Maintenance Periods

6.1.2.1. Titration Period Study Day 1

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

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

Site personnel will contact the subject via telephone on Titration period Study Days 4 and 8 and record the following:

- AEs
- AESI
- Concomitant medications

In addition, site personnel will review study medication dosing procedure and the diary entries with the parent/caregiver.

6.1.2.3. Clinic Visit 6 (Titration Period Study Day 15)

Subjects will report to the clinic in the morning on Titration period Study Day 15. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Obtain weight
- Obtain vital signs
- Collect, review, and dispense diary. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.
- C-SSRS Since Last Visit Assessment (Appendix 2)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (assessed by Investigator)
- Record AEs
  - Perform an abbreviated physical and/or neurological examination as appropriate based on last exam and reported AEs
  - Collect plasma sample for AED pharmacokinetic evaluation if clinically indicated (must document time of last dose)

- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.1.2.4. Phone Visit 7 (Maintenance Period Study Day 29)

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

- AEs
- AESI
- Concomitant medications

In addition, site personnel will review the diary entries with the parent/caregiver. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.

6.1.2.5. Clinic Visit 8 (Maintenance Period Study Day 43)

- Subjects will report to the clinic in the morning on Maintenance period Study Day 43. Subjects should not take their morning dose(s) of study medication. The following procedures will be performed:
- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Obtain weight **(Note: if the subject's weight is ±25% of the weight at Study Day -1, the IMP dose will be recalculated)**
- Obtain vital signs
- 12-lead electrocardiogram
- Doppler ECHO (this must be obtained any time between Study Day 40 and Study Day 54)
- Urine or serum pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, hematology, immunoglobulin, hormones, and urinalysis (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))
- Urine or serum THC panel
- Whole blood CBD
- Collect plasma sample for ZX008 pharmacokinetic evaluation at the following timepoints: within 1 hour prior to the morning dose of study medication, and 1, 2 and 4-6 hours after the morning dose of study medication
- Collect plasma sample for AED pharmacokinetic evaluation (must document time of last dose)
- Collect, review, and dispense diary. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.

- C-SSRS Since Last Visit Assessment (Appendix 2)
- VABS (Appendix 4)
- Zarit Caregiver Burden Inventory (Appendix 8)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (assessed by Investigator)
- Perform an abbreviated physical and/or neurological examination as appropriate based on last exam and reported AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.1.2.6. Phone Visit 9 (Maintenance Period Study Day 57)

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

- AEs
- AESI
- Concomitant medications

In addition, site personnel with review the diary entries with the parent/caregiver. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.

6.1.2.7. Clinic Visit 10 (Maintenance Period Study Day 71)

Subjects will report to the clinic on Maintenance period Study Day 71. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Obtain weight
- Obtain vital signs
- Collect, review, and dispense diary. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.
- C-SSRS Since Last Visit Assessment (Appendix 2)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (assessed by Investigator)
- Record AEs
- Perform an abbreviated physical and/or neurological examination as appropriate based on last exam and reported AEs
- Collect plasma sample for AED pharmacokinetic evaluation if clinically indicated

- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

At Clinic Visit 10, compliant subjects who have tolerated IMP should be presented with the ICF for the open-label extension (Part 2). Informed consent for the open-label extension should be signed at Visit 12 or earlier in order to enter the open-label extension.

6.1.2.8. Phone Visit 11 (Maintenance Period Study Day 85)

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

- AEs
- AESI
- Concomitant Medications

In addition, site personnel with review the diary entries with the parent/caregiver. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.

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

The End-of-Study participation in Part 1 for an individual subject occurs after he/she has received IMP for 12 weeks in the Maintenance period. At the Part 1 End-of-Study visit, the subject may enroll into the Part 2 OLE Treatment period if they have completed 12 weeks of treatment in the Maintenance period. Other circumstances for participation in Part 2 are described in Section 4.3. Informed consent for the Part 2 OLE Treatment period should be signed before data collection begins on Visit 12 (if not signed earlier) in order to participate in Part 2.

The End-of-Study visit may also occur if the subject withdraws participation from the study or the Sponsor terminates the study. If the subject withdraws participation from the study, they may on a case-by-case basis, be eligible for entrance into the Part 2 OLE Treatment period after consideration of the circumstances of the early termination and the potential benefit- risk of continued participation in a ZX008 trial. The decision whether to permit Part 2 participation resides solely with the Sponsor, who may consult with the site Investigator. If the Sponsor terminates the study early, the subject may or may not be offered enrollment into Part 2, depending on the reason for termination.

Subjects will visit the clinic for the End-of-Study visit if one the following events occur:

1. The subject withdraws or is withdrawn from participation in the study.
2. The Sponsor terminates the study.

The subject completes all study related visits and procedures. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Complete physical examination, including height and weight
- Complete neurological examination
- Obtain vital signs
- 12-lead electrocardiogram
- Doppler ECHO (must be performed any time between Study Day 90 and Study Day 113; if subject terminates early from the study, the ECHO should be scheduled as soon as practical). If the Study Day 43 ECHO was completed ≤30 days prior to early termination, the Visit 12 ECHO will not be performed provided the parent/guardian agrees to bring the subject to the clinic for the cardiac follow-up visit (see Table 9).
- For subjects enrolled in France or Netherlands only: conduct a chest x-ray
- Urine or serum pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, hematology, immunoglobulin, hormones, and urinalysis (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))
- Urine or serum THC panel
- Whole blood CBD
- Collect plasma sample for AED pharmacokinetic evaluation (must document time of last dose)
- Tanner Staging for subjects >7 to 18 years of age (Appendix 5)
- Collect, review, and dispense diary. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.
- C-SSRS Since Last Visit Assessment (Appendix 2)
- Clinical Global Impression – Improvement (assessed by parent/caregiver)
- Clinical Global Impression – Improvement (assessed by Investigator)
- BRIEF (Appendix 3)
- VABS (Appendix 4)
- QOLCE (Appendix 6)
- HADS (Appendix 7)
- Zarit Caregiver Burden Inventory (Appendix 8)
- Record AEs
- Record AESIs

- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication for taper for subjects not continuing into Part 2.

- Dispense and administer study medication for transition for subjects continuing into Part 2.

6.1.3. Post-Dose Visit (Clinic Visit 13; Study Day 113)

For subjects entering the Part 2 OLE Treatment period, the subject will visit the clinic on Day 113, which will also be Part 2 Day 1. The procedures described in Section 6.2 will be followed.

If the subject does not enter the Part 2 OLE Treatment period (or discontinues from the study early), the subject will visit the clinic on Study Day 113 (or 14 days after the day of discontinuation). If necessary, Visit 13 may be conducted as a phone call, provided diaries and study medication are returned by this time. The following will be recorded/performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- AEs
- AESIs
- Concomitant medications
- Collect and review diary with parent/caregiver
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

6.1.4. Cardiac Follow-Up Visit (Clinic Visit 14; 3-24 months after last dose depending on regional requirements)

If the subject completes the study but does not enter the Part 2 OLE Treatment period or discontinues from the study early, the subject will return to the clinic after study drug discontinuation for follow-up cardiac testing. The timing and frequency of exams are in Table 9. Subjects on blinded medication who are found to have been on placebo are not required to participate in follow-up testing once the blind is broken. As the ECHO and ECG will be administered in a separate clinic than the pediatric neurology clinic, an asymptomatic subject receiving a follow-up ECHO and ECG does not require a physical examination.

Subjects with positive findings on safety evaluations at post-dose follow-ups should have repeat examinations every 3 months until the finding is resolved or stable and unlikely to change, with reports submitted as AEs to the ZX008 safety database.

Table 9: Schedule of Post-Treatment Cardiac Follow-up for Part 1

Parameter	Duration of Blinded[a] or Fenfluramine Treatment			
	Less than 2 weeks Cumulative	**2 and <13 weeks**	**>13 weeks**	**Have had any cardiac sign or symptom regardless of the time on study drug[b]**
ECHO and ECG	No follow-up	Follow-up 3 months post-treatment	Follow-up 3 and 6 months post-treatment[c] in Germany, France, Netherlands: additional 24-month follow-up	Follow-up 3-24 months post- treatment[c], and every 3 months until resolved, or stable and unlikely to change
Physical examination	No follow-up	Follow-up 3 months post-treatment	Follow-up 3 months post- treatment only	Follow-up 3 months post- treatment, and every 3 months until resolved, or stable and unlikely to change
Chest x-ray (subjects enrolled in France or Netherlands only)	No follow-up	Follow-up 3 months post-treatment	Follow-up 3, 6, and 24 months post-treatment	Follow-up 3, 6, and 24 months post-treatment and every 3 months until resolved, or stable and unlikely to change

[a] If blind is broken at the end of the study and a subject revealed to have taken only placebo, no further testing is required.
[b] Positive sign or symptom includes any development of valve thickening or regurgitation (mild or greater in aortic; moderate or greater in mitral, pulmonary, tricuspid), or sign or symptom indicative of potential pulmonary hypertension as adjudicated by the ICAB.
[c] 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.

6.2. PART 2

Only eligible subjects as specified by the inclusion and exclusion criteria who have successfully completed Part 1, or have permission from the Sponsor, will be enrolled into Part 2. Other circumstances for participation in Part 2 are described in Section 4.3.

Review of inclusion and exclusion criteria and written informed parental or guardian consent and assent of minors (if the subject is capable of providing assent) for Part 2 must be obtained before a subject can start any of the Part 2 Visit 15 procedures. This includes review and approval (or adjudication if required) of the ECG and/or ECHO findings by the central reader, and approval for continuation in the open-label extension (if applicable) by the IDSMC.

Study procedures for the Part 2 OLE Treatment period will be conducted according to the Schedule of Assessments in Table 2. Time windows for all assessments are detailed in Table 10.

Table 10: Time Windows for Assessments in Part 2

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 15 (Clinic; OLE Study Day 1)	± 4 days[a]
Visits 16 (Clinic/Phone; OLE Study Day 15)	± 3 days
Visits 17-21 (Clinic: OLE Study Days 30, 60, 90, 180, 270)	± 4 days
Visit 22 (Clinic; OLE Study Day 365; EOS)	± 4 days
Visit 23 (Clinic; OLE Study Day 379; post dosing)	± 4 days
Visit 24, 25 (ECHO clinic; 3-24 months after last dose[b])	+ 30 days

Abbreviations: AED=antiepileptic drug (s); ECHO=echocardiogram

[a] In the case of a required safety review of a Visit 12 ECHO alert, the transition period between Visit 12 and Vist 15 may be extended up to 14 days to allow time for adjudication.

[b] Depending on country requirements. See Table 11 for details.

6.2.1. Clinic Visit 15 (OLE Study Day 1)

Part 2 Visit 15 will occur 14 days (± 4 days) after Part 1 Visit 12. The 14-day transition period preceding Visit 15 may be extended up to 14 days in the case of a required safety adjudication of a Visit 12 ECHO alert.

The following procedures will be performed during Visit 15:

- Ensure entry criteria for Part 2 are met
- Vital signs
- Record prior and concomitant medications (use core study Visit 12 information)
- Instruct parent/caregiver on use of diary
- Record ongoing AEs as medical history
- Record ongoing AESI as medical history
- Collect, review, and dispense diary (after above procedures have been concluded)
- Dispense study medication

Data collected from Part 1 Visit 12 may be used for the following procedures unless otherwise indicated:

- Record medical, neurological, and epilepsy history
- Complete physical examination, including height and weight (use data collected at Part 1 Visit 12, unless there was a significant change in subject status warranting a new complete examination)
- Complete neurological examination (use data collected at Part 1 Visit 12, unless there was a significant change in subject status warranting a new complete examination)
- 12-lead ECG
- Doppler ECHO
- For subjects enrolled in Italy only: conduct routine EEG
- Laboratory evaluation (serum chemistry, hematology, immunoglobulin, hormones, and urinalysis) (use Part 1 Visit 12 information, unless Investigator determines new laboratory evaluation is warranted due to change in subject status) (if collecting urine for

urinalysis, urine may be collected at home, the night before the clinic visit, as long as collection procedures are followed to maintain sample stability)
- Urine or serum pregnancy test for females of child-bearing potential
- Urine or serum THC panel
- Whole blood CBD
- C-SSRS Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by Investigator)
- BRIEF (Appendix 3)
- VABS (Appendix 4)
- QOLCE (Appendix 6)
- HADS (Appendix 7)
- Zarit Caregiver Burden Inventory (Appendix 8)

6.2.2. Clinic/Phone Visit 16 (OLE Study Day 15)

Part 2 Visit 16 may be performed in the clinic, or, at the discretion of the Investigator, performed via phone.

If Visit 16 is performed in the clinic, subjects will report to the clinic in the morning of that day. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications since previous visit
- Obtain weight
- Vital signs
- Laboratory evaluation (serum chemistry, hematology, immunoglobulin, hormones, and urinalysis) (only if Investigator determines new laboratory evaluation is warranted due to change in subject status since Visit 15) (if collecting urine for urinalysis, urine may be collected at home, the night before the clinic visit, as long as collection procedures are followed to maintain sample stability)
- Collect, review, and dispense diary. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.
- Record AEs
  - Perform an abbreviated physical and/or neurological examination as appropriate based on last exam and reported AEs
  - Collect plasma sample for AED pharmacokinetic evaluation if clinically indicated (must document time of last dose)
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Collect and review study medication

If the visit is performed as a phone visit, site personnel will contact the subject on Study Day 15 and record/review the following:

- Concomitant medications

- AEs
- AESI
- Study medication use
- Diary entries

6.2.3. Clinic Visits 17-21 (OLE Months, 1, 2, 3, 6, and 9)

Subjects will report to the clinic in the morning of Part 2 Clinic Visits 17 through 21. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Obtain weight (**Note: if the subject's weight is ±25% of the weight at Part 2 Day 15, the IMP dose will be recalculated**)
- Obtain vital signs
- 12-lead ECG
- Doppler ECHO (at Months 1, 3, 6, and 9)
- For subjects enrolled in Italy only: conduct routine EEG during Month 3
- Urine or serum pregnancy test for females of child-bearing potential (at Months 3, 6, and 9)
- Laboratory evaluation (serum chemistry, hematology, immunoglobulin, hormones, and urinalysis; at Months 3, 6 and 9 unless otherwise clinically indicated) (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)
- Urine or serum THC panel (at Months 3, 6 and 9)
- Whole blood CBD (at Months 3, 6, and 9)
- Collect plasma sample for AED PK and document time of last dose (at Months 3, 6, and 9 unless otherwise clinically indicated)
- Tanner Staging for subjects > 7 to 18 years of age (Month 6 only) (Appendix 5)
- Collect, review, and dispense diary. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.
- C-SSRS Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by Investigator)
- BRIEF (Month 6 only) (Appendix 3)
- QOLCE (Month 6 only) (Appendix 6)
- HADS (Month 6 only) (Appendix 7)
- Record AEs
    - Perform an abbreviated physical and/or neurological examination as appropriate based on last exam and reported AEs
    - Collect plasma sample for AED pharmacokinetic evaluation if clinically indicated
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.2.4. Clinic Visit 22; Study Day 365 (OLE Month 12): End of Study/Early Termination

The End-of-Study participation in Part 2 for an individual subject occurs after he/she has received IMP for 1 year in the Part 2 OLE Treatment period. The End-of-Study visit may also occur if the subject withdraws participation from Part 2 or the Sponsor terminates the study. If ZX008 is not commercially available for the treatment of seizures associated with LGS after the end of the OLE Treatment period, subjects may continue to receive ZX008 in a separate extension protocol. Continuation will be based on benefit/risk and will be offered to subjects who continue to meet eligibility requirements and comply with Investigator's instructions.

Subjects will visit the clinic for the End-of-Study visit if one the following events occur:

1. The subject withdraws or is withdrawn from participation in the study.
2. The Sponsor terminates the study.
3. The subject completes all study related visits and procedures.

The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Complete physical examination, including height and weight, and calculation of BMI
- Complete neurological examination
- Obtain vital signs
- 12-lead ECG
- Doppler ECHO (must be performed any time between Study Day 344 and Study Day 365; if subject terminates early from the study, the ECHO should be scheduled as soon as practical). If the Month 3, 6, or 9 ECHO was completed ≤ 30 days prior to early termination, the Visit 8 ECHO will not be performed provided the parent/guardian agrees to bring the subject to the clinic for the cardiac follow-up visit (see Table 11).
- For subjects enrolled in Italy only: conduct routine EEG
- For subjects enrolled in France or Netherlands only: conduct chest x-ray
- Urine or serum pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, hematology, immunoglobulin, hormones, and urinalysis) (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)
- Urine or serum THC panel
- Whole blood CBD
- Collect plasma sample for AED PK evaluation (must document time of last dose)
- Tanner Staging for subjects > 7 to 18 years of age (Appendix 5)
- Collect and review diary with parent/caregiver
- Collect, review, and dispense diary. Ensure diary is being completed daily; if diary compliance is low (ie, <90%), re-train parent/caregiver.
- C-SSRS Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by Investigator)
- BRIEF (Appendix 3)

- QOLCE (Appendix 6)
- HADS (Appendix 7)
- Zarit Caregiver Burden Inventory (Appendix 8)
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.2.5. Post-Dose Visit (Clinic Visit 23; Study Day 379)

If the subject completes the study (or discontinues from the study early), the subject will visit the clinic on Study Day 379 (or 14 days after the day of discontinuation) and the following procedures will be performed. Visit 23 may be conducted as a phone call if physical and neurological examinations are not clinically indicated, provided diaries and study medication are returned by this time.

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record AEs
  - Perform an abbreviated physical and/or neurological examination as appropriate based on last exam and reported AEs
- Obtain weight
- Record AESI
- Record concomitant medications
- Collect and review diary with parent/caregiver
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

6.2.6. Cardiac Follow-up Visit (Clinical Visit 24, 25; 3-24 months after last dose of IMP)

If the subject completes Part 2 or discontinues from the Part 2 early, the subject will return to the clinic for follow-up cardiac testing. The timing and frequency of exams are in Table 11. As the ECHO and ECG will be administered in a separate clinic than the pediatric neurology clinic, an asymptomatic subject receiving a second follow-up ECHO and ECG does not require a physical examination.

Subjects with positive findings on safety follow-up examinations should continue to be followed until the finding is resolved or stable and unlikely to change, with reports submitted as AE.

Table 11. Schedule of Post-Treatment Cardiac Follow-up for Part 2

Parameter	Duration of Fenfluramine Treatment			
	Less than 2 weeks Cumulative	**2 and ≤ 13 weeks**	**> 13 weeks**	**Have had any cardiac sign or symptom regardless of the time on study drug[a]**
ECHO and ECG	No follow-up	Follow-up 3 months post-treatment	Follow-up 3 and 6 months[b] post-treatment in Germany, France, Netherlands: additional 24 month follow-up	Follow-up 3 to 24 months[b] post-treatment, and until resolved, or stable and unlikely to change
Physical examination	No follow-up	Follow-up 3 months post-treatment	Yes, 3 months post- treatment only	Follow-up 3 months post-treatment, and until resolved, or stable and unlikely to change
Chest x-ray (subjects enrolled in France or Netherlands only)	No follow-up	Follow-up 3 months post-treatment	Follow-up 3, 6, and 24 months post-treatment	Follow-up 3, 6, and 24 months post-treatment and every 3 months until resolved, or stable and unlikely to change

[a] Positive sign or symptom includes any development of valve thickening or regurgitation ("mild" or greater in aortic; moderate or greater in mitral, pulmonary, tricuspid), or sign or symptom indicative of potential pulmonary hypertension as adjudicated by the ICAB.

[b] All subjects are required to have follow-ups at 3 and 6 months. Subjects enrolled in Germany, France and Netherlands will have an additional 24 month follow-up.

6.3. STUDY CONDUCT DURING COVID-19

In March 2020, the World Health Organization declared a global pandemic related to an illness caused by a novel coronavirus known as COVID-19. Alternative procedures and allowances are permitted due to restrictions related to COVID-19, including delays to in-person visits and specific assessments, performing remote phone or video visits if in-person visits cannot be conducted, and arranging shipments of investigational product directly to subjects. These allowances are detailed in Appendix 10. Though every attempt should be made to conduct study visits as described in this protocol, any implementation of alternative processes should be properly documented, including what was done differently, which assessments or visits were missed or performed via phone or video.

6.4. ESTIMATED BLOOD VOLUME COLLECTION

The maximum total blood volume collected during Part 1 of the study for clinical laboratory testing, genotyping, and PK will be approximately 84.0 mL, as outlined in Table 12. The maximum total blood volume collected during Part 2 of the study for clinical laboratory testing and PK will be approximately 74.0 mL, as outlined in Table 13.

Table 12: Maximum Estimated Blood Volume Collection for Part 1

PART 1	Visit 1 (Day -28)	Visit 3 (Day -1)	Visit 8 (Day 43)	Visit 12 (Day 99)	TOTAL
Coagulation		3.0 mL			3.0 mL
Chemistry	5.0 mL	5.0 mL	5.0 mL	5.0 mL	20.0 mL
Pregnancy test (serum)	included in Chemistry	included in Chemistry	included in Chemistry	included in Chemistry	0.0 mL
Hormones		5.0 mL	5.0 mL	5.0 mL	15.0 mL
Immunoglobulin	2.5 mL	2.5 mL	2.5 mL	2.5 mL	10.0 mL
Hematology	2.0 mL	2.0 mL	2.0 mL	2.0 mL	8.0 mL
Genotype Panel		4.0 mL			4.0 mL
AED PK plasma sample*		2.0 mL	2.0 mL	2.0 mL	6.0 mL
ZX008 PK plasma sample			8.0 mL		8.0 mL
Volume for flushing indwelling catheter			2.0		2.0 mL
Cannabidiol/THC	2.0 mL	2.0 mL	2.0 mL	2.0 mL	8.0 mL
TOTAL	11.5 mL	25.5 mL	28.5 mL	18.5 mL	**84.0 mL**

Abbreviations: AED=Anti-epileptic drugs; PK=pharmacokinetics
*Blood collection for AED pharmacokinetic evaluation may be collected on Visits 6 and 10 if clinically indicated. If collected during these visits, the total blood volume per subject would equal up to 88.0 mL.

Table 13. Maximum Estimated Blood Volume Collection for Part 2*

PART 2	Visit 19 (Day 90)	Visit 20 (Day 180)	Visit 21 (Day 270)	Visit 22 (Day 365)	TOTAL
Chemistry	5.0 mL	5.0 mL	5.0 mL	5.0 mL	20.0 mL
Pregnancy test (serum)	included in Chemistry	included in Chemistry	included in Chemistry	included in Chemistry	0.0 mL
Hormones	5.0 mL	5.0 mL	5.0 mL	5.0 mL	20.0 mL
Immunoglobulin	2.5 mL	2.5 mL	2.5 mL	2.5 mL	10.0 mL
Hematology	2.0 mL	2.0 mL	2.0 mL	2.0 mL	8.0 mL
AED PK plasma sample	2.0 mL	2.0 mL	2.0 mL	2.0 mL	8.0 mL
Cannabidiol/THC	2.0 mL	2.0 mL	2.0 mL	2.0 mL	8.0 mL
TOTAL	18.5 mL	18.5 mL	18.5 mL	18.5 mL	**74.0 mL**

AED=Anti-epileptic drugs; PK=pharmacokinetics
*Laboratory testing may be conducted on Visits 15-18 if clinically indicated. If collected during these visits, the total blood volume per subject would equal up to 111.0 mL.

*In concordance with The Seattle Children's Research Foundation Guidance (Appendix 9), blood collection volumes for children weighing up to 15 kg will be:

- The maximum allowable volume of blood in one draw is 22-30 mL (2.5% of total blood volume)
- The maximum in a 30-day period is 44 to 60 mL.

On Part 1 Day 43/Visit 8 the pharmacokinetic blood draw will be completed as the priority and the blood draw for chemistry and hematology will be skipped for those subjects who weigh less than 13.5 kg, unless medical concerns (for example, from previous tests or reported side effects) prioritize chemistry and/or hematology.

If blood collection is restricted due to volume or due to inability to draw adequate volume, collection should be prioritized as shown in Table 14.

Table 14: Priorities for Blood Sample Collections

Assessment	**Priority**
ZX008 PK sample	Priority 1
Clinical chemistry	Priority 2
Cannabidiol	Priority 2
AED plasma sample	Priority 2
LH, FSH, estradiol, testosterone, GH, prolactin	Priority 3
Hematology	Priority 3
IGF-1	Priority 4
Genotyping	One-time optional collection any time during or after Visit 3 (Randomization) in Part 1
Coagulation	One-time collection any time before Part 1 PK day

7. EFFICACY, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

For an overview of the study variables and measurement times, see Schedule of Assessments (Table 1 and Table 2).

Variables used to measure treatment compliance with respect to administration of the IMP are described in Section 5.7.

7.1. EFFICACY/EFFECTIVENESS ASSESSMENTS

Baseline is defined as the frequency of motor seizures resulting in drops during the 4-week Baseline period prior to administration of IMP.

Retrospective diary data (up to 6 months) will be collected, if available, for an exploratory evaluation of the duration of baseline data capture on interpretation of post-treatment effect.

For all questionnaires and rating scales, the same evaluator (at the clinical site and parent/caregiver) should complete the assessments for the duration of the study. Substitutions at the clinic with another rater that has established inter-rater reliability is acceptable on an infrequent basis. For the in-clinic questionnaires and rating scales completed by the parent/caregiver, if the same parent/caregiver cannot complete the questionnaire/rating scale at a visit, the questionnaire/rating scale will not be completed. For the diary, the same parent/caregiver will complete all entries throughout the study.

7.1.1. Seizure Assessments

Seizure frequency by type and duration will be recorded daily by the parent/caregiver in a diary. Seizure types include:

A: Hemiclonic (note lateralization – right body, left body, or independent right and left)
B: Focal With or Without Retained Awareness
C: Secondarily Generalized Tonic Clonic (evolving to bilateral convulsive seizure from focal seizure)
D: Generalized Tonic Clonic Convulsion
E: Absence or Atypical Absence
F: Myoclonic
G: Tonic
H: Atonic
I: Clonic
J: Tonic/Atonic (cannot differentiate)
K: Infantile Spasms (if under 3 years of age)
L: Epileptic Spasms (if 3 years of age and older)
O: Other*

* "Other" indicates a seizure type that cannot be classified in any of the above seizure types A-L. All seizures must be classified appropriately based on the Investigator's medical opinion and Epilepsy Study Consortium approval.

Parents/caregivers will also indicate in the diary entry whether the seizure resulted in a drop, or would have resulted in a drop were it not for the position (ie, in a chair). This includes seizures involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the

subject's head hitting a surface or that could have led to a fall or injury, depending on the patient's position at the time of the seizure.

Efficacy/effectiveness endpoints that will be derived from the diary data include frequency of seizures that result in drops and seizures that do not result in drops, motor seizures, and all seizures, and the number/duration of seizure-free intervals.

Seizures that evolve into status epilepticus (SE) will be captured by type and duration (>10 minutes) as are all seizures. SE should be entered as an SAE if a prolonged seizure or series of seizures persists for 30 minutes or longer, regardless of administration of rescue medication, *and* is either diagnosed by a medical professional or occurs more than once in a day. SE lasting for less than 30 minutes should be entered as an AE, unless one of the other SAE criteria (eg, hospitalization) are met. If this incident involves multiple seizures close in time, the SE definition applies if the seizures are close together such that consciousness is not regained between ictal events.

7.1.2. Clinical Global Impression - Improvement

Both the parent/caregiver and the Investigator will rate their global impression of the subject's condition throughout the study according to the schedule in Table 1 and Table 2.

The CGI scale measures the change in the subject's clinical status from a specific point in time, ie, the Baseline period. The CGI rating scale permits a global evaluation of the subject's improvement over time. The severity of a patient's condition is rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) as follows:

1=very much improved
2=much improved
3=minimally improved
4= no change
5=minimally worse
6=much worse
7=very much worse

The parent/caregiver will be asked to indicate the appropriate response that adequately describes how their child's symptoms have improved or worsened relative to baseline before the beginning of the study (before any study drug was taken).

The Investigator (or appropriately trained designee) will be asked to indicate the appropriate response that adequately describes how the subject's symptoms have improved or worsened relative to baseline before the beginning of the study (before any study drug was taken). A paragraph describing symptoms and function at baseline will be document in the source file prior to rating.

7.1.3. Vineland Adaptive Behavior Scale (VABS)

The VABS (Appendix 4) is a parent/caregiver completed assessment that looks at the personal and social skills of individuals from birth through adulthood. 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, and will be conducted according to the schedule in Table 1.

7.1.4. Quality of Life in Childhood Epilepsy (QOLCE)

The QOLCE (Appendix 6) is a parent/caregiver completed assessment that looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, well-being, cognition, social activities, behavior and general health, will be conducted according to the schedule in Table 1 and Table 2. The QOLCE has been validated in children aged 4 and older, and there are published data on the use of the QOLCE in children with epilepsy as young as 2 years of age (Sabaz 2000; Talarska 2007).

7.1.5. Parent/Caregiver Affective Symptoms

The impact on anxiety and depressive symptoms of the parent/caregiver responsible for a patient with LGS will be assessed according to the schedule in Table 1 and Table 2 using 2 scales: the HADS and the Zarit Caregiver Burden Inventory. Parents/caregivers who do not give consent to collect this rating scale will not complete them. The same parent/caregiver should complete this rating throughout the study. If that person is not available at the visit, the scale should not be completed.

7.1.6. Hospital Anxiety and Depression Scale (HADS)

The HADS (Appendix 7) is a tool commonly used to determine the levels of anxiety and depression that a person is experiencing. It is a 14-item scale that generates ordinal data. Seven of the items relate to anxiety and 7 relate to depression.

7.1.7. Zarit Caregiver Burden Inventory

The impact on caregiver burden will be assessed according to the schedule in Table 1 and Table 2 using the Zarit Caregiver Burden Inventory. Parents/caregivers who do not give consent to collect this rating scale will not complete them. The same parent/caregiver should complete this rating throughout the study. If that person is not available at the visit, the scale should not be completed.

The Zarit Caregiver Burden Inventory (Appendix 8) is a 22-item inventory derived from the original 29-item Zarit inventory. It is the most widely used standardized, validated scale to assess caregiver burden, administered previously in various neurological disorders, including epilepsy (Kim 2010; Westphal-Guitti 2007). The 22 items evaluate the effect of disease on the caregiver's QOL, psychological suffering, financial difficulty, shame, guilt, and difficulty in social and family relationships. Scores range from 0 to 88 with higher scores indicating higher burden (<20: little or no burden, 21–40: mild-to-moderate burden, 41–60: moderate-to severe burden, 61–88: severe burden).

7.2. SAFETY ASSESSMENTS

7.2.1. Demographics, Medical/Neurological/Epilepsy History, and Pre-Study Medication

Subject demographics (sex, age, height, weight, and BMI), all ongoing conditions and relevant medical history from the past 5 years (including all major hospitalizations and surgeries) as well as the subject's current medical status will be recorded at the Screening visit. Significant medications taken during the 30 days prior to the Screening visit will be documented.

Medication history will be updated as outlined in Table 1 and Table 2.

7.2.2. Adverse Events

Adverse events (AEs) will be collected from the time of signing the informed consent form/assent form until the end of the study, including the follow-up clinic visit. Details of the definitions and categorization of AEs, and procedures for the reporting of AEs, are available in Section 9.

Severity and causality of AEs will be evaluated according to the criteria specified in Section 8.2 and Section 8.3, respectively. The observation period for AE reporting is specified in Section 8.4. At the beginning of each visit at the study site, the study personnel will specifically inquire about any AEs that might have occurred since the last study site visit. As described below, an abbreviated physical and/or neurological examination for each subject will be conducted based on reported AEs. All AEs will be recorded on the appropriate eCRF page.

7.2.3. Physical Examinations

Complete and abbreviated physical examinations, including height and weight, will be conducted by the Investigator or designee during the study as outlined in Table 1 and Table 2. A complete standard of care physical examination for each subject will be performed and will cover the following body systems: general appearance, skin, eyes, ears, nose, throat, heart, lungs, abdomen, neurological system, lymph nodes, spine, and extremities. An abbreviated physical examination for each subject will cover the following body systems: heart, lungs, and follow up of other systems as appropriate based on last exam and reported AEs.

Any unfavorable findings not present at screening, or worsened from the baseline assessment and considered by the Investigator as clinically significant, occurring at any point in the study will be documented in the eCRF as an AE.

7.2.4. Neurological Examinations

Complete and abbreviated neurological examination will be conducted by the Investigator or designee during the study as outlined in Table 1 and Table 2. A complete standard of care neurological examination for each subject will be performed and will cover the following: cranial nerves, muscle strength and tone, reflexes, coordination, sensory function, and gait. An abbreviated neurological follow-up examination for each subject will evaluate any symptoms or systems found to be abnormal and unstable or potentially unstable that might evolve during study treatment, or to investigate any reported or observed AEs.

Any unfavorable findings not present at screening, or worsened from the baseline assessment and considered by the Investigator as clinically significant, occurring at any point in the study will be documented in the eCRF as an AE.

7.2.5. Vital Signs (Including Height and Weight)

Height, weight, and vital signs (blood pressure, heart rate, temperature, and respiratory rate) will be documented for subjects during study as outlined in Table 1 and Table 2.

7.2.6. Laboratory Measurements

Laboratory safety parameters will be analyzed using standard validated methods.

The following parameters will be assessed by the laboratory as described in Table 1, Table 2 and Table 9:

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

The Investigator will receive the laboratory report from the central laboratory. After reviewing the report and evaluating any results that are outside the normal range for clinical significance, the Investigator must sign and date the laboratory report in a timely fashion.

Tests resulting in abnormal laboratory values that have been classified by the Investigator as abnormal, clinically significant should be repeated as soon as possible after receiving the laboratory report to rule out laboratory errors.

At Screening, any laboratory values that deviate from the reference ranges that are not exclusionary and are considered by the Investigator as clinically relevant must be documented on the medical history form of the eCRF. Any deviation outside of the reference range considered by the Investigator as clinically significant (ie, classified as an abnormal, clinically significant value) at any visit after screening will be documented in the eCRF as an AE (see Section 9).

7.2.7. Plasma Sample for Concomitant Antiepileptic Drug(s)

Plasma samples to ensure that concomitant AEDs dosing is within an acceptable range will be conducted during the study as outlined in Table 1 and Table 2. All samples will be analyzed at study end and do not constitute safety assessments. (Importantly, plasma samples for concomitant AEDs can be performed at any time if considered clinically indicated. In these instances, results will be provided to the unblinded Medical Monitor and discussed with the Principal Investigator.)

7.2.8. Electrocardiograms

Twelve-lead ECGs will be conducted during study as outlined in Table 1 and Table 2 after the subject has been in the supine position resting for ≥5 minutes. Heart rate, PR duration, QRS duration, QT duration, QTcF (Fridericia's correction formula), and the Investigator's overall interpretation will be recorded.

7.2.9. Doppler Echocardiography

Doppler echocardiography will be conducted at a facility with experience for the subject's age during study as outlined in Table 1 and Table 2. Doppler echocardiography uses ultrasound technology to examine the heart or blood vessels. An ECHO uses high frequency sound waves to create an image of the heart while the use of Doppler technology allows determination of the speed and direction of blood flow by utilizing the Doppler effect. Predetermined standard guidelines on the proper evaluation of certain measurements, as well as abnormality thresholds, were constructed by the Sponsor's ICAB prior to study initiation. These thresholds are provided in Table 11. A manual of proper ECHO technique for sites is provided in a separate document.

7.2.10. Chest X-ray (France and Netherlands only)

For subjects enrolled in France and Netherlands only, an anterior/posterior chest x-ray will be obtained as outlined in Table 1 and Table 2.

7.2.11. Electroencephalogram (EEG) (Italy only)

Routine electroencephalogram (r-EEG) will be conducted during visits 15, 19, and 22 at centers in Italy only. The potential for EEG to induce seizures should be considered and if a patient is determined to be at high risk for EEG-induced seizure, then EEG should not be conducted. Standard clinical measures should be in place to mitigate against EEG-induced seizure. As these EEGs are considered exploratory, they should be locally read and stored in the site files. EEG recordings will not be captured in the CRF.

7.2.12. Behavior Rating Inventory of Executive Function (BRIEF)

The Behavior Rating Inventory of Executive Function (BRIEF) is a parent or teacher report measure designed to address the multidimensional nature of the executive function construct and will be used to assess the effects of ZX008 on cognition. The BRIEF assesses eight theoretically and statistically derived subdomains of executive function. It was designed to be used for a wide range of childhood disorders in order to augment traditional clinic-based assessments, and to provide an increased level of ecological validity for clinical assessments (Rabbit 1997). Age-appropriate versions of the BRIEF (BRIEF-P: 2- to 5-year-olds; BRIEF: 6- to 18-year-olds; BRIEF-A: 19- to 35-year-olds), will be conducted according to the schedule in Table 1.

7.2.13. Tanner Staging

Tanner Staging (Appendix 5) will be assessed for subjects >7 to 18 years old during the study as outlined in Table 1 and Table 2. Conceptually, pubertal maturation can be described in terms of sequence, timing, and tempo. Puberty consists of a series of predictable events, and the sequence of changes in secondary sexual characteristics has been categorized by several groups. The staging system used most frequently was published by Marshall and Tanner (1969, 1970) and the sequence of changes are commonly referred to as 'Tanner stages'.

7.2.14. Columbia-Suicide Severity Rating Scale

C-SSRS (Appendix 2) will be assessed during study as outlined in Table 1 and Table 2. The C-SSRS is a validated rating scale that assesses suicidal behavior and ideation. The scale is used to assess and track suicide events and provides a summary measure of suicidal tendency. Age and intellectual development appropriate versions of the C-SSRS (Baseline/Screening and Since Last Visit) will be used in this study.

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.

7.3. PHARMACOKINETIC ASSESSMENTS

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

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

- Part 1 Study Day 43: within 1 hour prior to the morning dose, and 1 (± 15 min), 2 (± 15 min), and 4-6 hours after the morning dose.

A total of 4 PK samples will be drawn for each subject for a total of approximately 8 mL of blood.

When blood draws for PK coincide with other assessments, the PK draws take precedence.

The procedure for the collection and handling of PK samples is outlined in a separate study manual.

7.4. EPILEPSY GENOTYPE PANEL

Optional blood samples for genetic analysis are being collected for a comprehensive analysis for a broad epilepsy gene panel that will be analyzed at the end of the study to investigate genetic characteristics of study responders and nonresponders. Whole genome sequencing is not being performed. Testing is restricted to a 377 childhood epilepsy gene panel; thus, the risk of revealing clinically relevant or medically actionable incidental findings is low. Samples may be retained for up to 24 months after the end of the study.

The field of genetics related to epileptic encephalopathies are developing rapidly, thus, in the event that new theories emerge on the genetics associated with LGS, the retained samples might be used to investigate this genotype in the study population. Results of genetic testing will only be provided upon written request; therefore, unless required by law individual results of genotyping will not be disseminated outside of the Sponsor, including to the study site. Genotyping samples will be double-coded (pseudonymized) so that it is impossible to trace back the personal identifying information from the sample number.

7.5. APPROPRIATENESS OF MEASUREMENTS

All of the variables assessed are standard tests or procedures that are commonly used in studies of this type.

8. ADVERSE EVENTS

8.1. DEFINITIONS

8.1.1. Adverse Events

According to ICH guidelines, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. The period of observation for adverse events extends from the time the subject gives informed consent until the end of study.

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study. Exacerbation of seizures is considered an AE if there was an increase in frequency beyond the subject's typical pre-study fluctuations, or in the event that seizures lengthen in duration in a clinically meaningful way compared with baseline, or if a new seizure type emerges.
- A clinical event occurring after consent but before IMP administration.
- Intercurrent illnesses with an onset after administration of IMP.

Adverse events do not include:

- Medical or surgical procedures (the condition that leads to the procedure is the AE, eg, tonsillitis is the AE if a tonsillectomy is performed)
- Situations where an untoward medical occurrence has not taken place. For example:
- Planned hospitalizations due to pre-existing conditions, which have not worsened.
- Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery).
- Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal management procedures (eg, chemotherapy).

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the Investigator as clinically significant must be recorded in the eCRF as AEs. In addition, at the Investigator’s discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

1. Laboratory parameters are already beyond the reference range, unless a further increase/decrease can be considered an exacerbation of a pre-existing condition.

2. Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, hemolysis) and flagged as such by the laboratory in the laboratory report.
3. Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life).
4. An abnormal laboratory value that cannot be confirmed after a repeated analysis, preferably in the same laboratory (eg, the previous result could be marked as not valid and should not necessarily be reported as an AE).

8.1.2. Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

1. **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.
2. **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
3. **Requires in-patient hospitalization or prolongation of existing hospitalization** – The Sponsor considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, chemotherapy) are not considered as defining criteria for SAEs.
4. **Results in persistent or significant disability or incapacity**.
5. **Is a congenital anomaly or birth defect.**
6. **Is medically significant** – A medically significant event is defined as an event that does not meet any of the other 5 SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion. Anaphylaxis that is successfully treated by administration of epinephrine prior to other sequelae is an example of a potentially medically important event.

The most important term should be selected as the criteria for the SAE. Medically significant should be used when none of the other terms apply.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are defined as SAEs that do not meet determination of expectedness as determined in accordance with applicable product information (Investigator's Brochure or other reference documentation). Upon receipt of a SAE report from an Investigator site, all suspected adverse reactions related to the IMP which occur within the clinical trial will be assessed for expectedness. Any SAE not listed in the reference documentation is considered a Suspected Unexpected Serious Adverse Reaction (SUSAR). SUSARs will be reported by the Sponsor, or its designee, in compliance with local legal requirements. During the course of the study, the Sponsor will report within required timelines all SAEs that are both unexpected and at least reasonably related to the IMP (SUSARs) to the Health Authorities, IECs / IRBs as appropriate and to the Investigators. This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [1994]).

For the purpose of data collection in this study, a prolonged seizure or series of seizures from which the subject does not regain consciousness between ictal events, that is at least

30 minutes in duration, is termed status epilepticus (SE). SE should be entered as an SAE if a prolonged seizure or series of seizures persists for 30 minutes or longer, regardless of administration of rescue medication, *and* is either diagnosed by a medical professional or occurs more than once in a day. SE lasting for less than 30 minutes should be entered as an AE, unless one of the other SAE criteria (eg, hospitalization) are met. If this incident involves multiple seizures close in time, the SE definition applies if the seizures are close together such that consciousness is not regained between ictal events.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

8.1.3. Adverse Events of Special Interest

As per ICH guidance (E2F Development Safety Update Report [2011]), the Sponsor has identified the following AESIs for the ZX008 program (Table 15).

Table 15: 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

8.2. SEVERITY OF ADVERSE EVENTS

The severity of AEs (whether nonserious or serious AEs) is to be assessed by the Investigator as follows (Table 16).

Table 16: Severity Definition of Adverse Events

Severity	Definition
Mild:	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe:	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.3. CAUSALITY OF ADVERSE EVENTS

The causal relationship of an AE to IMP must always be assessed by the Investigator. All AEs will be classified as either **related** or **not related** to IMP. If a causality assessment is not provided for an AE (including an SAE), that AE will be considered as related to IMP.

The degree of certainty with which an AE is attributed to IMP or an alternative cause (eg, natural history of the underlying disease, concomitant medication) will be determined by how well the event can be understood in terms of:

- Known pharmacology of ZX008
- Clinically and/or pathophysiologically plausible context
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor)
- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with IMP drug withdrawal or reproduced on rechallenge)

The following classifications should be used in categorization of relatedness:

Not Related:	Concomitant illness, accident or event with no reasonable association with study drug.
Related:	The event follows a reasonable temporal sequence from administration of study drug and is definitive pharmacologically; cannot to be attributed to concurrent disease or other factors or medications. A clinically reasonable response should be observed if the study drug is withdrawn or dose reduced.

8.4. OBSERVATION PERIOD FOR ADVERSE EVENT REPORTING

The observation period for AE and SAE reporting in an individual subject will start at the time of giving written informed consent for participation in the current study and finish 15 days after the last dose of study drug or the last visit, whichever is later. For subjects who enroll in the open-label extension (Part 2), ongoing AEs will be followed in that study.

If the Investigator becomes aware of an SAE that has started after the observation period has finished, and the event could in some way be associated with IMP (irrespective of whether or not it is considered by the Investigator to be causally related to IMP), then this must also be reported to the Sponsor (see Section 8.6).

8.5. ADVERSE EVENT REPORTING

8.5.1. Adverse Events

At each clinical evaluation, the Investigator (or delegate) will determine whether any AEs have occurred. Adverse events will be recorded in the AE page of the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms. The Investigator must follow up on the course of an AE until resolution or

stabilization. If an AE is ongoing after the end of study visit, the AE will continue to be followed up until resolution or stabilization.

If, during the study period, a subject presents with a pre-existing condition that was not noted at the time of study entry, the condition should be retrospectively recorded in the Medical History section of the eCRF.

8.6. SERIOUS ADVERSE EVENTS REPORTING

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [1994]).

In the event of a SAE the Investigator or delegate must:

1. Enter all relevant information in the AE page of the eCRF
2. Inform the safety group and/or the Medical Monitor of the SAE via email or fax within 24 hours of becoming aware of the SAE.
3. Follow the initial notification with a completed SAE report form. The SAE form must be emailed or faxed to IHC within 24 hours of becoming aware of the SAE.

All SAEs that occur during the course of the study, beginning the day Informed Consent is signed, whether or not causally related to IMP must be reported immediately via fax or email (within 24 hours of the Investigator becoming aware of the event) to the Sponsor/designee or the Medical Monitor.

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

Any SAE that occurs 15 days after the last dose of study drug or the last visit, whichever is later that is considered to be causally related to IMP must be **reported immediately (ie, within 24 hours of the Investigator becoming aware of the event) to the Sponsor/designee and the Medical Monitor**.

Contact details and guidance for reporting SAEs will be provided to study site before the study starts.

8.6.1. Requirements for Immediate Reporting of Serious Adverse Events

The minimum reporting requirements for immediate reporting of SAEs include:

1. Identifiable subject
2. Suspected drug product
3. Event description
4. Identifiable reporting source

In addition, the Investigator must:

1. Report all SAEs to the relevant IRB/IEC within the timeframe specified by the IRB/IEC.

2. Submit follow-up reports to the Sponsor Global Clinical Safety and Pharmacovigilance/designee and the Medical Monitor until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
3. Ensure that the AE term(s) and causality assessment for all SAEs is entered in the eCRF.

If the minimum requirements for reporting are fulfilled, the Investigator should not wait to receive additional information to fully document the event before notifying the Sponsor/designee.

When submitting SAE reports to the Sponsor/designee, subjects should be identified only by their subject number and study number. The Investigator should not include the subject's name and address.

SAE update reports can be submitted to the Sponsor/designee any time that additional relevant information becomes available. In cases of death, the Investigator should supply the Sponsor/designee and the IEC/IRB (as applicable, see Section 8.7) with any additional requested information as it becomes available (eg, autopsy reports and detailed medical reports). Once an SAE is reported to the Sponsor/designee's Safety Group, a Safety Specialist may contact the Investigator with follow-up questions.

The procedure to be followed if an ongoing AE becomes an SAE after the end of the observation period for AEs is described in Section 8.9.

8.7. REPORTING OF SERIOUS ADVERSE EVENTS BY INVESTIGATOR TO IEC/IRB

The timeframe within an IEC/IRB must be notified of a death or an unexpected SAE considered at least possibly related to the IMP is stipulated by each individual IEC/IRB. The Investigator is responsible for complying with the requirements for IEC/IRB notification. The Investigator will notify the relevant IEC/IRB within the applicable timeframe by forwarding the safety report (eg, MedWatch/CIOMS form) completed by the Sponsor/designee for the notifiable event.

8.8. REPORTING OF EVENTS OTHER THAN SERIOUS ADVERSE EVENTS BY INVESTIGATOR TO SPONSOR

Even if none of the criteria for an SAE are fulfilled, any of the following events must be reported by the Investigator to the Medical Monitor within 72 hours from the time the Investigator is notified.

1. Hypersensitivity reactions
2. Pulmonary hypertension
3. Cardiac symptoms requiring intervention, or valvulopathy, if identified outside of study-related monitoring

8.9. FOLLOW-UP OF ADVERSE EVENTS

Every effort should be made to follow-up subjects who continue to experience an AE or an SAE on completion of the study or until the AE resolves. All follow-up information (and attempted follow-up contacts) should be documented in the subject's medical records. Details of the

subject's progress should also be submitted to the Sponsor/designee's Global Clinical Safety and Pharmacovigilance and the Medical Monitor.

Subjects who are discontinued from the study or complete the study and have been found to have any signs of valvulopathy or pulmonary hypertension on ECHO will be followed until the condition has resolved or stabilized where no further changes are likely, for a minimum of 6 months from the last dose of study medication, unless it is determined after unblinding that the subject did not receive ZX008.

8.9.1. Follow-up of Echocardiogram Findings

All ECHOs will be evaluated by a central reader, in consultation with the ICAB, if warranted. Findings related to pulmonary hypertension or valvulopathy on any of the four valves (aortic, mitral, pulmonary, tricuspid) will be reported to the Investigator with grades of normal, trace, mild, moderate or severe. If the ECHO result has progressed in severity since the last reading then new oversight measures will be enacted as described below in Levels 1 to 3. Table 17 describes the severity of ECHO findings with the level of increasing oversight if the subject is to remain in the study.

Table 17: Clinical Measures Enacted Upon Increasing Severity of ECHO Findings

	Valve			
Severity	**Aortic**	**Mitral**	**Pulmonary**	**Tricuspid**
Trace	Level 1	Level 1	Level 1	Level 1
Mild (≤18 years)	Level 2	Level 2	Level 1	Level 1
Mild (>18 years)	Level 2	Level 1	Level 1	Level 1
Moderate	Level 3	Level 3	Level 3	Level 3
Severe	Level 3	Level 3	Level 3	Level 3

Level 1: Continue per protocol

Level 2:

1. If there is a desire to continue study medication:
   a. The Investigator will evaluate the efficacy to date based on study diaries and consult with the parent/guardian, and determine whether study treatment was associated with significant, meaningful benefit in number, severity and/or duration of seizures and/or on the impact on daily functioning.
   b. The Investigator will consider whether the subject has had reasonable trials (dose and duration) of other available anticonvulsants (eg, valproic acid, clobazam, or topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.
2. If the Investigator feels consideration of continued treatment is warranted considering benefit and potential risk, and the parent/guardian feels strongly that the subject be maintained on the study medication when understanding the risks, the parent/guardian must sign a new consent which describes the additional risks and the subject should provide assent if appropriate.

a. If both of these conditions are not met, the subject is discontinued from treatment.

3. The Investigator prepares a case history and rationale for continuation to be submitted to the IDSMC for review, including consideration of effects on seizures and comorbidities.
4. The cardiac reviewers (from the central reader, and potentially ICAB) prepare an evaluation of the cardiopulmonary risks and proposed monitoring plan if applicable, for submission to the IDSMC.
5. IDMSC will review the submissions from the Investigator and cardiac central reader and unblind the subject treatment if warranted.
6. IDSMC makes a determination of appropriate path, including the possible outcomes:
   a. Discontinue study medication
   b. Increase frequency of ECHO and ECG monitoring
   c. Add additional ECG and/or ECHO measures to be monitored
   d. Reduce the dose of study medication

Level 3:

1. The Investigator will evaluate efficacy to date based on study diaries and consult with the parent/guardian, and determine whether the achieved benefit justifies the consideration of continuing study treatment by the IDSMC. MINIMAL efficacy criteria for IDSMC consideration:
   a. Seizures must be more than 75% improved (number of motor seizures per 28 days) on treatment over baseline, and improvement must be consistent.
   b. The number, type, duration, and distribution of seizures at baseline should be of a severity, which justifies the risks of cardiopulmonary complications, considering the subject's age and overall health.
   c. Subject has had reasonable trials (dose and duration) of other available anticonvulsants (eg, valproic acid, clobazam, topiramate), alone or in combination, and not maintained the level of seizure control achieved with study medication.
2. If the Investigator feels consideration of continued treatment is warranted considering benefit and potential risks, and the parent/guardian feels strongly that the child be maintained on the study medication when understanding the risks, the parent/guardian must sign a new consent, which describes the additional risks and the child should provide assent if possible.
   a. If both of these conditions are not met, the subject is discontinued from treatment.
3. The Investigator prepares a case history and rationale for continuation to be submitted to the IDSMC for review, which includes effects of study medication on seizures and comorbidities related to LGS.
4. The cardiac reviewers (from the central reader, and potentially ICAB) prepare an evaluation of the cardiopulmonary risks and proposed monitoring plan if applicable, for submission to the IDSMC.
5. IDMSC will review the submissions from the Investigator and cardiac central reader and unblind the subject treatment if warranted.
6. IDSMC makes a determination of appropriate path, including these possible outcomes:
   a. Discontinue study medication
   b. Increase frequency of ECHO and ECG monitoring
   c. Add additional ECG and/or ECHO measures to be monitored

8.10. PREGNANCY

This study is open to female and male subjects. Whenever possible, a pregnancy in female subjects or the female partner of a male subject exposed to IMP should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the Investigator to the Sponsor/designee using a pregnancy reporting/outcome form.

9. DATA HANDLING PROCEDURES

9.1. RECORDING OF DATA

The Investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, study-required information and data, and other notes as appropriate. These records constitute source data.

An eCRF and a subject diary will be provided by the Sponsor (or delegate) for each subject enrolled into the study. Study site staff will enter data directly into the validated electronic data capture (EDC) system by completing the eCRF via a secure internet connection. The Investigator is responsible for ensuring accurate and proper completion of the eCRF and subject diary for recording data according to the instructions given in the eCRF and subject diary.

All entries in the eCRF must be backed up by the relevant source data at the study site. All source data will be kept according to all applicable regulatory requirements (see Section 12.8). Source data must follow good documentation practices, be completed legibly for each subject enrolled into the study and signed by the Investigator (or delegate).

Data entry in the eCRF and subject diary must be completed in a timely manner so that they always reflect the latest observations on the subjects enrolled in the study.

The subject's diary will be completed by the parent/caregiver at home. Data entries will be reviewed by the Investigator for completion and consistency.

9.2. DATA QUALITY ASSURANCE

An initiation meeting will be held before starting the study, during which the study design, procedures to be followed, and measures for ensuring standardized performance will be explained by a delegate from the Sponsor, and a common understanding of the requirements of the study will be reached with the Investigator and other relevant personnel at the study site.

Data generated throughout the study will be monitored and the data entered in the eCRFs will be checked against the subject records for completeness and accuracy. The Sponsor's study monitor will perform this function.

The computer system used for study data handling will be fully FDA 21 CFR Part 11 compliant. All creation, modification or deletion of electronic study records will be documented through an automated Audit Trail. Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically for consistency and plausibility. Data queries will be generated for questionable data and response clarification will be sought from the Investigator. These data queries must be resolved in a timely manner by the Investigator (or delegate).

9.3. RECORD RETENTION

A study document binder will be provided by the Sponsor for the Investigator at each site for all requisite study documents (constituting the "Investigator Study File").

Following completion of the study, the Investigator will retain copies of the approved study protocol, ICF, relevant source documents, and all other supporting documentation related to the study according to applicable regulatory requirements.

The Investigator is responsible for archiving the Investigator Study File, the subject's records, and the source data according to applicable regulatory requirements. These documents have to be archived for at least 15 years or at least 2 years after the last approval of a marketing application in an ICH region, but should be retained for longer if required by regulatory requirements or by agreement with the Sponsor.

If the Investigator can no longer maintain the archive of study records (eg, due to retirement or relocation), the Sponsor must be informed in writing about any change in responsibility for record retention, including the name of the new responsible party, contact information, and location of the study records. Records may not be destroyed without prior written consent from the Sponsor.

10. STATISTICS

10.1. STATISTICAL ANALYSIS: PART 1

The primary analyses of the study will be performed on data from Part 1 Cohort A after the last subject enrolled in Cohort A has completed the last study visit of Part 1. A secondary analysis will be conducted after the last Cohort B subject has enrolled and completed the last study visit of Part 2. Analysis results for Part 1 from Cohort A and Cohort B will be compared through descriptive statistics, and if reasonable, some analysis may be performed using data from Cohort A and Cohort B combined. Subjects randomized to 0.5 mg/kg/day (ie, those taking concomitant STP) will be grouped with subjects randomized to 0.8 mg/kg/day for all efficacy analyses.

10.1.1. 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 SD is 50%. Other assumptions include an allowance for 20% dropouts between randomization and the start of the maintenance period.

Under these assumptions, and using a Wilcoxon rank-sum test to approximate the primary comparison between the ZX008 0.8 mg/kg/day and placebo groups, a sample size of 63 subjects per treatment group affords 90% power to detect a difference between 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 16 subjects per group for a total of 79 subjects per treatment group. 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.

The sample size of 10 to 15 subjects per treatment group in Cohort B is expected to provide a descriptive assessment of whether the treatment effect in Japanese subjects is similar that observed in Cohort A subjects from the rest of the world.

10.1.2. Analysis Populations

10.1.2.1. 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.

10.1.2.2. Modified Intent-to-Treat (mITT) Population

The mITT Population is defined as all randomized subjects who receive at least one dose of ZX008 or placebo and for whom at least one week of diary data are available. Subjects will be analyzed according to the treatment group to which they were randomized. The primary

comparison of ZDX008 0.8 mg/kg/day to placebo, as well as key secondary analyses, will be performed on the mITT Population.

10.1.2.3. Per Protocol (PP) Population

The PP Population is defined as all randomized subjects who receive at least one dose of ZX008 or placebo, who complete at least 4 weeks of diary data in the maintenance period, and have no major protocol deviations that would have a significant impact on clinical outcome.

10.1.3. Subject Cohorts

10.1.3.1. Cohort A

Cohort A comprises all randomized subjects from North America, Europe, and Australia.

10.1.3.2. Cohort B

Cohort B comprises all randomized subjects from Japan only.

10.1.4. Treatment Groups

Subjects will be randomly assigned to one of three treatment groups: ZX008 0.8 mg/kg/day, ZX008 0.2 mg/kg/day, or placebo.

10.1.5. Treatment Periods

Baseline Period

The Baseline period covers the 28 days immediately prior to randomization. The baseline frequency of seizures that lead to drops will be calculated from data collected during this period.

Titration Period

The Titration period covers the first 14 days of treatment while subjects are titrated to their randomized dose. It begins on the first full day of treatment (Study Day 1) and extends through Study Day 15 regardless of the exact day on which a subject reaches his or her assigned dose. The Titration period applies to all subjects including placebo recipients.

Maintenance Period

The Maintenance period covers the 12 weeks following the end of the titration period. It begins on Study Day 16 and extends through Study Day 99.

Titration +Maintenance (T+M) Period

The T+M period combines the Titration and Maintenance periods, beginning on Study Day 1 and extending through Study Day 99. The T+M period is considered the treatment period.

Taper/Transition Period

The Taper/Transition period begins immediately at the end of T+M period and extends to Visit 13, 2 weeks later; ie, from Study Day 99 through Study Day 113.

10.1.6. Statistical Analyses and Methods

All efficacy, safety, and PK data will be summarized by cohort. Continuous data will be summarized using descriptive statistics including means, standard deviations, medians, lower and upper quartiles, and ranges. Categorical variables will be summarized with frequencies and percentages. Confidence intervals will be calculated for key parameters or estimates as warranted.

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

10.1.6.1. Efficacy Analyses

Primary Efficacy Analysis

The primary efficacy endpoint for Part 1 is the percent change in frequency of seizures that result in drops (DSF: drop seizure frequency) per 28 days between the combined Titration and Maintenance (T+M) and Baseline periods in Cohort A. The DSF will be calculated from all available data collected during the Baseline and T+M periods without imputation. The percent change from baseline DSF will be calculated as the change in DSF between T+M and Baseline / DSF during Baseline× 100. Both the mean and median percent change in DSF will be presented.

The primary endpoint will be assessed using a nonparametric, rank analysis of covariance (ANCOVA) with treatment group (ZX008 0.8 mg/kg/day, ZX008 0.2 mg/kg/day or placebo) and weight group (<37.5 kg, ≥37.5 kg) as factors; rank baseline DSF as a covariate; and rank percent change in DSF from baseline as the response variable. The primary analysis will compare the ZX008 0.8 mg/kg/day group to the placebo group at the α=0.05 level of significance. The difference between the ZX008 0.8 mg/kg/day group and the placebo group in percent change in DSF, and its 95% confidence interval, will be estimated using the Hodges-Lehmann method.

As a sensitivity analysis, the primary endpoint will also be analyzed using a parametric ANCOVA that incorporates treatment group and weight group as factors; log baseline DSF as a covariate; and log DSF during T+M as the response variable. Significance will be assessed by a model contrast that compares the ZX008 0.8 mg/kg/day group to the placebo group. The size of the treatment effect will be estimated by exponentiating the difference between the ZX008 0.8 mg/kg/day group and the placebo group derived from the model. Another sensitivity analysis will compare the ZX008 0.8 mg/kg/day group to the placebo group using a Wilcoxon rank-sum test.

Key Secondary Analyses

The first key secondary endpoint for the ZX008 0.8 mg/kg/day group – the proportion of subjects who achieve a ≥50% reduction from baseline in the frequency of seizures that result in drops – is derived directly from the primary endpoint, but is widely considered a benchmark for clinical meaningfulness of a medical intervention for seizures. The comparison will be made using a logistic regression model that incorporates the same factors and covariate as the ANCOVA used in the primary analysis. The second key secondary endpoint – the proportion of subjects assessed by the Principal Investigator as minimally, much, or very much improved on the CGI-I – will be analyzed using a Cochran-Mantel-Haenszel test (CMH) stratified by weight strata.

The percent change from baseline DSF in the ZX008 0.2 mg/kg/day group will be compared to the placebo group using the same methods employed for the primary analysis. In particular, the same rank ANCOVA model will be used. Analyses of other key secondary endpoints involving the ZX008 0.2 mg/kg/day group will employ similar methods as those used to compare ZX008 0.8 mg/kg/day to placebo.

Multiplicity Strategy and Testing Hierarchy

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

The hierarchy starts with the primary analysis comparing ZX008 0.8 mg/kg/day to placebo on the percent change from baseline in DSF. The next two steps in the hierarchy also entail comparisons of ZX008 0.8 mg/kg/day to placebo on two key secondary endpoints. The last three steps in the hierarchy all involve comparisons of ZX008 0.2 mg/kg/day to 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 percent change from baseline in DSF.
2. Compare ZX008 0.8 mg/kg/day to placebo on the proportion of subjects who achieve a ≥50% reduction from baseline in DSF.
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 percent change from baseline in DSF.
5. Compare ZX008 0.2 mg/kg/day to placebo on the proportion of subjects who achieve a ≥50% reduction from baseline in DSF.
6. Compare ZX008 0.2 mg/kg/day to placebo on the CGI-I at Visit 12.

Part 1 Cohort B

Efficacy analyses for Part 1 Cohort B will use the same methods as described for Part 1 Cohort A. Some subsets analyses may not be feasible in Cohort B due to its smaller sample size.

10.1.6.2. Safety Analyses

Summaries of safety data will be presented by treatment – ZX008 0.8 mg/kg/day, ZX008 0.2 mg/kg/day or placebo – for the T+M period. The number and percentage of subjects in each treatment group with AEs will be displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs by severity and relationship to study drug will also be presented. A separate summary will be provided for all serious AEs (SAEs). If warranted, selected summaries will be repeated broken out by weight group, ie, for subjects who weigh <37.5 kg and those who weigh ≥37.5 kg.

Laboratory tests, vital signs, physical examinations, neurological examinations, ECG, Doppler echocardiogram, chest x-ray (France and Netherlands only), EEG (Italy only), C-SSRS, Tanner

Staging results, etc., will be summarized appropriately, by treatment. All safety summaries will be based on the SAF Population.

10.1.6.3. Pharmacokinetic Analyses

Model-derived plasma PK parameters of fenfluramine and norfenfluramine (C_{max_ss}, $Cmin_{\_ss}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}24}$) will be summarized descriptively by treatment group, when sufficient data are available. A population PK model, previously developed using data from healthy adults and pediatric patients with Dravet syndrome, will updated to include the fenfluramine and norfenfluramine concentration-time data collected during the Maintenance period. This model will be informed by all relevant data available at the time of data collection (both adults and pediatrics). The population mean and interindividual variability estimates from the fit of the PopPK model will be summarized. The results from the PopPK modeling will be reported separately and conducted according to a separate SAP.

10.2. STATISTICAL ANALYSIS: PART 2

Safety and effectiveness will be assessed in the subjects who continue into Part 2 of the study in which all subjects receive open-label ZX008.

10.2.1. Analysis Populations

10.2.1.1. OLE Population

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

10.2.1.2. OLE mITT Population

The OLE mITT Population is defined as all randomized subjects who receive at least one dose of ZX008 and have valid seizure data during the open label extension.

10.2.2. Treatment Groups

All subjects in Part 2 will receive ZX008 and will be considered a single treatment group. Selected data summaries may be broken out by the treatment received during Part 1 and/or average dose received during Part 2.

10.2.3. Treatment Periods

Open-Label Extension (OLE) Treatment Period

The OLE Treatment period covers the duration during which subjects receive open label treatment with ZX008.

OLE Taper Period

The OLE Taper period begins immediately after the OLE Treatment period and extends for 2 weeks.

10.2.4. Statistical Analyses and Methods

10.2.4.1. Safety Analyses

The number and percentage of subjects who experience treatment emergent AEs will be displayed by body system and preferred term using MedDRA. Summaries in terms of severity and relationship to study drug will also be provided. SAEs will be summarized separately in a similar manner. Laboratory tests, vital signs, physical examinations, neurological examinations, ECG, ECHO, chest x-ray (France and Netherlands only), EEG (Italy only), cognition and body weight will be summarized using appropriate methods.

10.2.4.2. Effectiveness Analyses

Effectiveness will be assessed by the change from baseline (prior to randomization into Part 1) in DSF. The DSF per 28 days will be calculated as the number of seizures recorded divided by the number of days in the period and multiplied by 28. The change in DSF during the OLE Treatment period will be calculated as the difference between DSF during the OLE and the baseline DSF measured prior to randomization in Part 1. The percent change in DSF is the change in DSF between OLE and Baseline / DSF during Baseline x 100. Both the mean and median percent change in DSF will be presented and the statistical significance of the percent change will be assessed using a Wilcoxon signed-rank test. Other secondary assessments will be compared to baseline from prior to Part 1, or by visit throughout Part 1 and Part 2, as appropriate.

10.2.5. Analyses Provided to an Independent Data and Safety Monitoring Committee

A safety oversight monitoring plan will be in place with an IDSMC evaluating data from the subjects. Details will be provided in the IDSMC charter. The IDSMC's primary responsibility is to ensure that study subjects are not exposed to unanticipated harm that could have been prevented by timely review and intervention. The IDSMC is established to review safety data at predefined time points, and to recommend to the Sponsor whether to continue, modify, or terminate the study as necessary. The IDSMC is composed of expert permanent members who cover relevant specialties. The IDSMC members may request assistance from a number of additional and ad hoc members if needed.

11. ETHICAL & REGULATORY CONSIDERATIONS

11.1. ETHICAL CONSIDERATIONS

The procedures set out in this study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 Guideline. ICH GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected and consistent with the principles of the Declaration of Helsinki, and that the clinical study data are credible.

The study will also be carried out according to all applicable international and national regulatory requirements.

The Sponsor and the Investigator must inform each other (eg, during a study initiation visit, via e-mail, etc.) that all ethical and legal requirements have been met before the first subject is enrolled into the study.

11.2. INFORMED CONSENT

The Investigator is responsible for obtaining a subject's written informed consent to participate in the study.

A Subject Information Sheet and a master ICF will be prepared by the Sponsor according to the provisions of ICH GCP and local legal requirements.

All subjects will be informed that the study will be registered in the public database at ClinicalTrials.gov in accordance with the FDA Amendments Act of 2007 (Section 12.3).

Before undergoing screening procedures for possible enrollment into the study, subjects must be informed, in an understandable form, about the nature, scope, and possible consequences of the study. This information must be given orally to subjects by a physician or medically qualified person (according to applicable regulatory requirements) who is well informed about the nature, scope, and possible consequences of the study. Written information about the study will also be provided in a Subject Information Sheet. The date on which this oral and written information on the study was provided to the subject, and by whom it was provided, must be documented in the ICF.

As specified in ICH GCP Section 4.8 and the US 21CFR Section 50.25, the informed consent discussion must emphasize that participation in the study is voluntary and that subjects have the right to withdraw their consent at any time without giving a reason and without any disadvantage for their subsequent care.

Subjects must be given ample time and opportunity to inquire about details of the study and to consider their participation in the study. If, after reading the Subject Information Sheet and the ICF, consent is given to participate in the study, then the ICF must be signed and personally dated by the subject and the person conducting the informed consent discussion (and an impartial witness, if required). The subject will be provided with a copy of the signed ICF.

Verification of the signed ICF will be recorded in the subject's eCRF. The original signed ICF will be filed with the subject's records and/or in the Investigator Study File.

The Subject Information Sheet and ICF have to be approved by the IEC/IRB before they can be used in the study.

The Subject Information Sheet and ICF must be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revision of these documents must be approved by the IEC/IRB before they can be used in the study. Subjects must be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation in the study. The communication of this information should be documented by having all parties concerned sign and personally date the revised ICF.

Subject or Subject's Legally Acceptable Representative Unable to Read

If a subject is unable to read, or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information provided to the subject, parent or guardian has been read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should also sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

Assent for Subjects Under the Age of Consent (Pediatric Subjects)

All subjects are under the age of consent (ie, pediatric subjects under 18 years of age); the written informed consent of a legally acceptable representative is required. Pediatric subjects who can understand the nature, scope, and possible consequences of the study must also give their assent, orally and/or in writing via the assent document, as appropriate. After the ICF and any other written information to be provided to subjects has been read and explained to the subject and the subject's legally acceptable representative, and after the subject and the legally acceptable representative have orally consented to the subject's participation in the study and, if capable of doing so, the subject has signed and personally dated the assent document, the legally acceptable representative should sign and personally date the ICF. By signing the ICF, the legally acceptable representative attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the subject, and that assent was freely given by the subject.

11.3. REGULATORY CONSIDERATIONS AND INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

The Sponsor (or delegate) will submit the appropriate documents to all applicable competent regulatory authorities and IEC/IRBs, and will await all relevant approval before enrolling any subjects into the study. Written approval should mention the study protocol by study title, study number, and version date.

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

The Sponsor (delegate) will ensure that the Investigators conduct the study as stipulated in this study protocol and in accordance with all applicable regulatory requirements. The Sponsor (delegate) is obliged to obtain evidence of the Investigator's qualification to perform the clinical study. Therefore, the Investigator has to provide a signed and dated copy of his or her professional curriculum vitae (prepared no more than 2 years beforehand and preferably written in English) before the start of the study, including information on his or her experience in conducting clinical studies according to ICH GCP and other applicable regulatory requirements.

Written notification of the identity and occupation of the members of the IEC/IRB is also required by the Sponsor (delegate). Should the IEC/IRB be unwilling to provide this information, a letter stating that the committee was constituted in accordance with applicable regulatory requirements should be provided.

11.4. PROTOCOL COMPLIANCE

The Investigator must conduct the study in compliance with this study protocol as agreed to by the Sponsor and, if required, by any competent regulatory authority, and which has been approved by, or given a favorable opinion by, the IEC/IRB.

The Investigator should not implement any deviation from, or changes to, the study protocol without agreement by the Sponsor (delegate) and prior review and documented approval or favorable opinion from the IEC/IRB of an amendment to the study protocol. Exceptions include only cases of medical emergency to address immediate hazards to study subjects, or when the changes involve only logistic or administrative aspects of the study.

In the event of a medical emergency, the Investigator at each site may institute any medical procedures deemed appropriate to address an immediate hazard to a subject without prior IEC/IRB approval or favorable opinion. As soon as possible, the implemented deviation or change, the reason(s) for it, and, if appropriate, the proposed study protocol amendment(s) should be submitted to:

- The Sponsor (delegate) for agreement.
- The IEC/IRB for review and approval or favorable opinion (if required).
- The applicable competent regulatory authority (if required).

Details of the procedure for implementing study protocol amendments are available in Section 12.10.

At the earliest opportunity, the Investigator (or delegate) must inform the Sponsor (delegate) about any notable protocol deviations and explain any deviation from the approved study protocol in the eCRF and/or in the Protocol Deviation Log, if applicable.

12. ADMINISTRATIVE ASPECTS

12.1. CLINICAL TRIAL AGREEMENT

This study will be conducted under a Clinical Trial Agreement between the Sponsor (or delegate) and the respective institutions representing the study sites. Any financial support given to the study sites will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement, which must be signed before the start of any study related procedures, will clearly delineate the responsibilities and obligations of the Investigator and the Sponsor (delegate), and will form the contractual basis upon which the study will be conducted.

12.2. FINANCIAL DISCLOSURE BY INVESTIGATOR

Prior to study initiation, the Investigator and any Sub-Investigator(s) to be directly involved in the treatment or evaluation of study subjects at each study site will disclose to the Sponsor (delegate) any relevant financial or proprietary interests in either the study product or the Sponsor company. The appropriate disclosure form(s) will be provided by the Sponsor (delegate) for this purpose. Any relevant updates to the financial disclosure information that occur during the conduct of the study, or during one year after completion of the study, will be provided by the Investigator and Sub-Investigator(s) to the Sponsor (delegate). All financial disclosure information provided by the Investigator and Sub-Investigator(s) will be submitted to appropriate competent authorities according to the applicable regulatory requirements.

12.3. CLINICAL STUDY REGISTRATION AND RESULTS DISCLOSURE

The Sponsor will provide the relevant study protocol information in a public database (ClinicalTrials.gov) before or at commencement of the study, as required by the 2007 FDA Amendments Act. The Sponsor (delegate) may also provide study information for inclusion in national registries according to local regulatory requirements.

If a potential subject contacts the Sponsor regarding participation in the study, the Investigator agrees that the Sponsor (delegate) may forward the relevant study site and contact details to the subject. Based on the inclusion and exclusion criteria for the study, the Investigator will assess the suitability of the subject for enrollment into the study. Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record on ClinicalTrials.gov.

12.4. STUDY FILES AND MATERIALS

Before the start of any study related procedures, all essential documents specified by ICH GCP and other applicable regulations must be available in the relevant files maintained by the Sponsor (or delegate) and the Investigator. An Investigator Study File prepared by the Sponsor (or delegate), containing all applicable documents for use at the study site, will be made available to the Investigator before the start of the study. A list of personnel and organizations responsible for conduct of the study as well as the list of Investigators will be included in the Investigator Study File. The respective files will be kept and updated by the Sponsor (or delegate) and the Investigator, as applicable.

All study documentation and materials maintained in the Investigator Study File at the study site must be available for inspection by the Sponsor's study monitor (or delegate) to determine that all required documentation is present and correct (see Section 12.9).

The study may be audited or inspected by qualified delegates from the Sponsor or a competent regulatory authority (see Section 12.11).

12.5. INITIATION OF THE STUDY

Before the start of the study at each study site, the Sponsor's study monitor (or delegate) will ensure adequacy of the facilities and discuss responsibilities regarding study protocol adherence with the Investigator and other personnel involved in the study.

The Investigator may not enroll any subjects into the study before the Sponsor has received written approval or a favorable opinion from the IEC/IRB for conducting the study and a formal meeting has been conducted by the Sponsor's study monitor (or delegate) to initiate the study (study initiation visit).

12.6. SUBJECT REIMBURSEMENT

Where relevant, subjects will be reimbursed for reasonable travel costs associated with participation in this study, after presentation of receipts for the travel in question, at a rate to be approved by the IEC/IRB. Subjects will not be paid for participating in the study.

12.7. LIABILITY AND INSURANCE

The civil liability of the involved parties with respect to financial loss due to personal injury and other damage that may arise as a result of this study being conducted are governed by the applicable legal requirement(s).

The Sponsor will provide insurance to the Investigator if required by the applicable regulatory and legal requirement(s).

If required by local law, subjects taking part in this study will be insured against any injury caused by the study in accordance with the applicable regulatory and legal requirement(s).

12.8. SUBJECT IDENTIFICATION AND CONFIDENTIALITY

All study documents, including the study protocol and eCRFs, are the confidential property of the Sponsor and should be treated as such.

All subjects screened for the study will be documented in a screening log in compliance with the requirements of individual study sites. Subjects not enrolled into the study will be documented as such in the screening log together with the reason for not having been enrolled.

The Investigator will maintain a personal list of subject names and subject numbers (Subject Identification List) for participants in the study to enable records to be identified at a later date. These records should be retained in a confidential manner for the duration stipulated by applicable regulatory requirements. All subject names will be kept in confidence and will not be revealed to the Sponsor. Subject names must be made unreadable on any documents made available to the Sponsor.

Subjects participating in the study will be identified in the eCRF by the subject number allotted to them during the study.

The ICF will include a statement that all study findings, irrespective of the medium on which they are stored, will be handled in strictest confidence in accordance with applicable data protection laws (eg, the European Data Protection Directive [95/46/EC] and the USA Health Insurance Portability and Accountability Act [HIPAA]), and will be evaluated by the Sponsor and/or a competent regulatory authority in an anonymized form. The subjects are also to be informed that their medical records may be audited or inspected by qualified delegates from the Sponsor or a competent regulatory authority. The subject's written consent authorizing direct access to his medical records, and computer processing and publishing of his anonymous personal data, must be obtained prior to participation in the study.

A subject's identity will be disclosed by the Investigator only in case of emergency (ie, to address any immediate health hazard).

12.9. MONITORING OF THE STUDY

The Investigator at each site will allow the Sponsor's study monitor (or delegate) reasonable access to the eCRFs and direct access to related source documents for monitoring purposes as frequently as the Sponsor deems necessary. These documents include records of tests performed as a requirement for participating in the study as well as other medical records required to confirm information contained in the eCRF, such as past history and secondary diagnoses.

Before each monitoring visit, the Investigator (or delegate) should record all data generated since the last monitoring visit in the eCRF. The Investigator and other relevant personnel at each study site will be expected to cooperate with the Sponsor's study monitor to assist in providing any missing information.

The study monitor will require access to the Investigator Study File to ensure completeness of all documentation required for the study. The study monitor will ensure that the Investigator at each site has been provided with adequate means for organization and filing of study documentation (see Section 12.4).

The date on which the study monitor (or delegate) visits the study site will be recorded in the Site Visit Log. During monitoring visits, the study site's coordinator (if applicable) and the Investigator should be available, the source documentation should be accessible, and a suitable environment should be provided for the study monitor to review study related documentation.

The main objectives of monitoring visits conducted by the study monitor include:

- Resolution of any problems.
- Examination of all study documentation for completion, adherence to the study protocol, and possible AEs.
- Clarification of inconsistencies or missing data.
- Verification of study data against source documents.
- Checks that Investigator obligations have been fulfilled.

- Review of ICFs and dates of consent.
- Inspection of IMP with respect to storage, labeling, and documentation.
- Drug accountability

After each subject's visit to the study site, the Investigator (or delegate) will ensure that all data have been entered into the eCRF correctly and in a timely manner, after which the Investigator will sign the eCRF.

12.10. PROTOCOL AMENDMENTS

A "substantial" amendment of a study protocol is any written description of change(s) to, or formal clarification of, a study protocol that may have a significant impact on the safety or physical or mental integrity of subjects, the scientific value of the study, the conduct or management of the study, or the quality or safety of any IMP used in the study. The IEC/IRB must approve all substantial protocol amendments prior to their implementation. If required by applicable local regulatory requirements, the local regulatory authority must also approve all substantial protocol amendments prior to their implementation.

A "nonsubstantial" amendment of a study protocol includes minor corrections or clarifications that have no significant impact on the way the study is to be conducted and has no effect on the safety of participating subjects (eg, change in study monitor, contact details, etc.). If required by applicable local regulatory requirements, the IEC/IRB, and/or the local regulatory authority should be notified of all nonsubstantial protocol amendments. The substantial and nonsubstantial protocol amendments will be integrated into an updated study protocol at the discretion of the Sponsor if the changes to the original study protocol are numerous, or if required by applicable regulatory requirements.

12.11. AUDITS AND INSPECTIONS

The study may be audited or inspected by qualified delegates from the Sponsor or a competent regulatory authority.

In the event of an audit by the Sponsor, the Investigator must make all study related documentation available to the auditor(s). Regulatory authorities may request access to all study related documentation, including source documents, for inspection and copying in keeping with applicable regulations. The Sponsor will immediately notify the Investigator (or vice versa) of an upcoming audit or inspection.

If an audit or inspection occurs, the Investigator and relevant personnel at the study site must allocate sufficient time to discuss the findings and any relevant issues.

12.12. CLINICAL STUDY REPORT

After completion of the study, a clinical study report covering clinical and statistical aspects of the study will be prepared by the Sponsor (or delegate) in consultation with the coordinating Investigator. As required by the applicable regulatory requirements, the clinical study report will be signed by the Sponsor's responsible medical officer as well as the coordinating Investigator (if applicable).

Progress reports and/or a summary of the clinical study report will be provided to the IEC/IRB and competent regulatory authorities in accordance with applicable requirements.

12.13. USE OF DATA AND PUBLICATIONS

The rights and obligations of Investigators and the Sponsor concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study (see Section 12.1).

For multicenter studies, the first publication must be based upon all data obtained from all analyses, as stipulated in the study protocol by the biostatistician and not by the Investigators. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of study sites before the full, initial publication is available or

5 years after the last clinical study visit, whichever is later, unless this has been agreed to by all other Investigators and by the Sponsor.

The Sponsor must receive a copy of any intended communications in advance of the proposed submission date. This is to allow the Sponsor time to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential and/or proprietary information is not inadvertently divulged, to provide any relevant supplementary information, and to allow establishment of co-authorship (as appropriate). The authorship of communications arising from pooled data will include Investigators from study sites that contributed data as well as relevant personnel from the Sponsor. Ownership of all data will remain with the Sponsor.

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14. APPENDICES

APPENDIX 1 – LIST OF PROHIBITED CONCOMITANT MEDICATIONS

The below table lists examples of medications in the classes prohibited under the exclusion criteria defined in the protocol, but it is not an exhaustive list. Please consult the medical monitor in your region if a participant is on a medication that falls into any prohibited classifications but is not listed in the below table.

ADHD Medications			
Atomoxetine	Amphetamine and derivates	Methamphetamine	Guanfacine
Methylphenidate		Lisdexamfetamine	Bupropion
Dexmethylphenidate	Dextroamphetamine	Clonidine	
Anti-arrhythmics	**Antibiotics**	**Anti-nausea**	**Anti-pyretic**
Mexiletine	Linezolid	Metoclopramide	Phenacetin
Propafenone		Ondansetron	
Anticonvulsants			
Felbamate**	Retigabine/ezogabine	THC and derivatives	
Epidiolex	Cannabidiol products		
Antidepressants (SSRIs, SNRIs, NRIs)			
Amitriptyline	Clomipramine	Fluvoxamine	Paroxetine
Bupropion	Desipramine	Imipramine	Sertraline
Buspirone	Duloxetine	Nefazodone	Trazodone
Citalopram	Fluoxetine	Nortriptyline	Vortioxetine
Antihistamines			
Astemizole	Hydroxyzine	Chlorphenamine	
Cyproheptadine	Cetirizine	Diphenhydramine	
Anti-migraine			
Almotriptan	Eletriptan	Naratriptan	Sumatriptan
Cafergot	Ergotamine tartrate	Rizatriptan	Zolmitriptan
Antipsychotics/Neuroleptics (serotonin agonists/ antagonists, noradrenergic agonists/antagonists)			
Amisulpride	Guanfacine	Paliperidone	Risperidone
Amphetamine	Haloperidol	Perospirone	Sulpiride
Aripiprazole	Levomepromazine	Perphenazine	Ziprasidone
Asenapine	Lurasidone	Promethazine	Zuclopenthixol
Clozapine	Methylphenidate	Propanolol	
Clonidine	Olanzapine	Quetiapine	
Anti-viral	**Beta Blocker**	**Chemotherapy**	**Cough Suppressant**
Interferon	Alprenolol	Dasatinib	Dextromethorphan
Ritonavir	Bufuralol		
Telaprevir			
Centrally-acting anorectic agents			
Lorcaserin	Phentermine	Naltrexone-bupropion	Phentermine-topiramate
Diethylpropion	Benzphetamine	Phendimetrazine	
Decongestants (allowed for short-term use only)		**Statins**	
Phenylpropanolamine		Cerivastatin	

Ergot Alkaloids, their derivatives, and Antiparkinson agents			
Pergolide	Cabergoline	Ergotamine Tartrate	
Monoamine-oxidase inhibitors			
Isocarboxazid	Selegiline	Tranylcypromine	Phenelzine
Opioids			
Alfentanil	Levacetylmethadol (LAAM)	Meperidine	Oxycodone
Codeine	Fentanyl	Methadone	Tramadol

**Felbamate is prohibited as a concomitant medication unless the subject has been on felbamate for at least 12 months prior to screening, has stable liver function and hematology laboratory tests, the dose has been stable for at least 60 days prior to screening and is expected to remain constant throughout the study.

APPENDIX 2 – COLUMBIA – SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline/Screening

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION				
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime**		**Past 6 Months**	
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
INTENSITY OF IDEATION *The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).* ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe		Most Severe	
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	___		___	

 C-SSRS—Children's Baseline/Screening (Version 6/23/10) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as there are separate events: must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** *Did you_____ as a way to end your life?* *Did you want to die (even a little) when you_____?* *Were you trying to make yourself not alive anymore when you_____?* *Or did you think it was possible you could have died from_____?* ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-injurious Behavior without suicidal intent) If yes, describe:	Yes No ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes No ☐ ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self; gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops himherself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding, sprains). 2. Moderate physical damage: medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage: *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage: *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code*	*Enter Code*	*Enter Code*
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

 C-SSRS – Children's Baseline/Screening (Version 6/23/10) Page 2 of 2

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

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

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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

APPENDIX 3 – BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION

BRIEF®-P

Behavior Rating Inventory of Executive Function®– Preschool Version

RATING FORM

Gerard A. Gioia, PhD, Kimberly Andrews Espy, PhD, and Peter K. Isquith, PhD

Instructions to Parents and Teachers

On the following pages is a list of statements that describe young children. We would like to know if the child has had *problems* with these behaviors *during the past 6 months*. Please answer *all the items* the best that you can. Please do not skip any items. Think about the child as you read these statements and circle:

N if the behavior is **Never** a problem
S if the behavior is **Sometimes** a problem
O if the behavior is **Often** a problem

For example, if having tantrums when told "No" is **never** a problem, you would circle **N** for this item:

Has tantrums when told "No" (N) S O

If you make a mistake or want to change your answer, ***DO NOT ERASE***. Instead draw an **X** through the answer you want to change and then circle the correct answer:

Has tantrums when told "No" (X) (S) O

Before you begin answering the items, please fill in the child's name, gender, age, and birth date, as well as your name, relationship to the child, and today's date in the spaces provided at the top of the next page. If you are the child's teacher or child care provider, please check the box next to the response that best describes how well you know the child and indicate how long you have known the child in the space provided.

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Child's Name _____ Gender _____ Age _____ Birth Date ___/___/___

Your Name _____ Today's Date ___/___/___

Relationship to Child: ☐ Mother ☐ Father ☐ Teacher* ☐ Other* _____

How well do you know the child? ☐ Not Well ☐ Moderately Well ☐ Very Well *Have known the child for____ ☐ months ☐ years.

During the past 6 months, how often has each of the following behaviors been a *problem*?	Never	Sometimes	Often
1. Overreacts to small problems	N	S	O
2. When given two things to do, remembers only the first or last	N	S	O
3. Is unaware of how his/her behavior affects or bothers others	N	S	O
4. When instructed to clean up, puts things away in a disorganized, random way	N	S	O
5. Becomes upset with new situations	N	S	O
6. Has explosive, angry outbursts	N	S	O
7. Has trouble carrying out the actions needed to complete tasks (such as trying one puzzle piece at a time, cleaning up to earn a reward)	N	S	O
8. Does not stop laughing at funny things or events when others stop	N	S	O
9. Needs to be told to begin a task even when willing to do it	N	S	O
10. Has trouble adjusting to new people (such as babysitter, teacher, friend, or day care worker)	N	S	O
11. Becomes upset too easily	N	S	O
12. Has trouble concentrating on games, puzzles, or play activities	N	S	O
13. Has to be more closely supervised than similar playmates	N	S	O
14. When sent to get something, forgets what he/she is supposed to get	N	S	O
15. Is upset by a change in plans or routine (for example, order of daily activities, adding last minute errands to schedule, change in driving route to store)	N	S	O
16. Has outbursts for little reason	N	S	O
17. Repeats the same mistakes over and over even after help is given	N	S	O
18. Acts wilder or sillier than others in groups (such as birthday parties, play group)	N	S	O
19. Cannot find clothes, shoes, toys, or books even when he/she has been given specific instructions	N	S	O
20. Takes a long time to feel comfortable in new places or situations (such as visiting distant relatives or new friends)	N	S	O
21. Mood changes frequently	N	S	O
22. Makes silly mistakes on things he/she can do	N	S	O
23. Is fidgety, restless, or squirmy	N	S	O
24. Has trouble following established routines for sleeping, eating, or play activities	N	S	O
25. Is bothered by loud noises, bright lights, or certain smells	N	S	O
26. Small events trigger big reactions	N	S	O
27. Has trouble with activities or tasks that have more than one step	N	S	O
28. Is impulsive	N	S	O
29. Has trouble thinking of a different way to solve a problem or complete an activity when stuck	N	S	O
30. Is disturbed by changes in the environment (such as new furniture, things in room moved around, or new clothes)	N	S	O

During the past 6 months, how often has each of the following behaviors been a *problem*?	Never	Sometimes	Often
31. Angry or tearful outbursts are intense but end suddenly	N	S	O
32. Needs help from adult to stay on task	N	S	O
33. Does not notice when his/her behavior causes negative reactions	N	S	O
34. Leaves messes that others have to clean up even after instruction	N	S	O
35. Has trouble changing activities	N	S	O
36. Reacts more strongly to situations than other children	N	S	O
37. Forgets what he/she is doing in the middle of an activity	N	S	O
38. Does not realize that certain actions bother others	N	S	O
39. Gets caught up in the small details of a task or situation and misses the main idea	N	S	O
40. Has trouble "joining in" at unfamiliar social events (such as birthday parties, picnics, holiday gatherings)	N	S	O
41. Is easily overwhelmed or overstimulated by typical daily activities	N	S	O
42. Has trouble finishing tasks (such as games, puzzles, pretend play activities)	N	S	O
43. Gets out of control more than playmates	N	S	O
44. Cannot find things in room or play area even when given specific instructions	N	S	O
45. Resists change of routine, foods, places, etc.	N	S	O
46. After having a problem, will stay disappointed for a long time	N	S	O
47. Cannot stay on the same topic when talking	N	S	O
48. Talks or plays too loudly	N	S	O
49. Does not complete tasks even after given directions	N	S	O
50. Acts overwhelmed or overstimulated in crowded, busy situations (such as lots of noise, activity, or people)	N	S	O
51. Has trouble getting started on activities or tasks even after instructed	N	S	O
52. Acts too wild or out of control	N	S	O
53. Does not try as hard as his/her ability on activities	N	S	O
54. Has trouble putting the brakes on his/her actions even after being asked	N	S	O
55. Unable to finish describing an event, person, or story	N	S	O
56. Completes tasks or activities too quickly	N	S	O
57. Is unaware when he/she does well and not well	N	S	O
58. Gets easily sidetracked during activities	N	S	O
59. Has trouble remembering something, even after a brief period of time	N	S	O
60. Becomes too silly	N	S	O
61. Has a short attention span	N	S	O
62. Plays carelessly or recklessly in situations where he/she could be hurt (such as playground, swimming pool)	N	S	O
63. Is unaware when he/she performs a task right or wrong	N	S	O

BRIEF-P Preschool Scoring Summary

Date ____/____/____

Child's Name _____ Gender _____ Age _____ Relation of Rater to Child _____

Scoring Instructions

1. Remove the perforated stubs from the Rating Form and detach the answer sheet to reveal the Scoring Sheet.
2. Transfer the circled item score for each item to the box provided in that item row.
3. Sum the item scores in each column and enter the subtotal in the box at the bottom of the column.
4. Transfer the scale subtotals for Items 1-30 to the appropriate box in the row for subtotals at the bottom of the facing page.
5. Sum the two subtotals for each scale and enter the total in the Total scale raw scores box.
6. Transfer each scale raw score to the raw score column in the Scoring Summary Table below.
7. Sum the raw scores for Inhibit and Emotional Control (EC) to obtain the raw score for the Inhibitory Self-Control Index (*ISCI*).
8. Sum the raw scores for Shift and Emotional Control (EC) to obtain the raw score for the Flexibility Index (*FI*).
9. Sum the raw scores for Working Memory (WM) and Plan/Organize (PO) to obtain the raw score for the Emergent Metacognition Index (*EMI*).
10. Sum the raw scores for the five scales (Inhibit + Shift + EC + WM + PO) to obtain the raw score for the Global Executive Composite (*GEC*).
11. Locate the norms tables for the appropriate normative comparison group in the Appendix tables of the BRIEF-P Professional Manual. Find the raw score for each scale, index, and *GEC* in the raw score column and read across the row to find the corresponding *T* score and percentile. Enter the *T* score and percentile in the appropriate boxes in the Scoring Summary Table. Locate the 90% Confidence Interval (CI) value for each scale, index, and *GEC* at the bottom of the appropriate column, calculate the low end (subtract the CI value from the *T* score) and high end (add the CI value to the *T* score) of the interval, and enter those values in the spaces provided in the 90% CI column.

Scoring Summary Table

Scale/Index	Raw score	*T* score	%ile	90% CI
Inhibit				____ – ____
Shift				____ – ____
Emotional Control (EC)				____ – ____
Working Memory (WM)				____ – ____
Plan/Organize (PO)				____ – ____
ISCI (Inhibit + EC)				____ – ____
FI (Shift + EC)				____ – ____
EMI (WM + PO)				____ – ____
GEC (Inhibit + Shift + EC + WM + PO)				____ – ____

Negativity Scale

1. Negativity items are indicated with a [N] in the margin of the Scoring Sheet. For each Negativity item with a score of 3, circle that item number in the column to the right.
2. Count the number of circled item numbers to determine the **Negativity score**.
3. Using the Negativity Score table below, circle the appropriate protocol classification corresponding to that score.

Negativity score	Cumulative %	
	Parent	Teacher
0 – 2	0 – 97 Acceptable	0 – 98 Acceptable
3	98 – 99 Acceptable	99 Elevated
≥4	100 Elevated	100 Elevated

Item
30.
44.
46.
47.
53.
55.
56.
57.
59.
63.
Negativity score

Inconsistency Scale

For each item pair:

1. Transfer the item score for each item (marked (1) in the margin of the Scoring Sheet) to the appropriate item pairs box.
2. Subtract the ***lesser*** number from the ***greater*** number and enter the result in the *Difference* column.
3. Sum the numbers in the *Difference* column to obtain the **Inconsistency score**. Circle the appropriate protocol classification corresponding to that score in the table below.

Inconsistency score	Cumulative %	
	Parent	Teacher
0 – 6	0 – 94 Acceptable	0 – 98 Acceptable
7	97 – 98 Acceptable	99 Inconsistent
≥8	99 – 100 Inconsistent	100 Inconsistent

Item	Score	Item	Score		Difference
1.		11.		→	
3.		33.		→	
5.		45.		→	
10.		20.		→	
11.		26.		→	
16.		21.		→	
18.		52.		→	
33.		38.		→	
43.		52.		→	
48.		54.		→	
				Inconsistency score	

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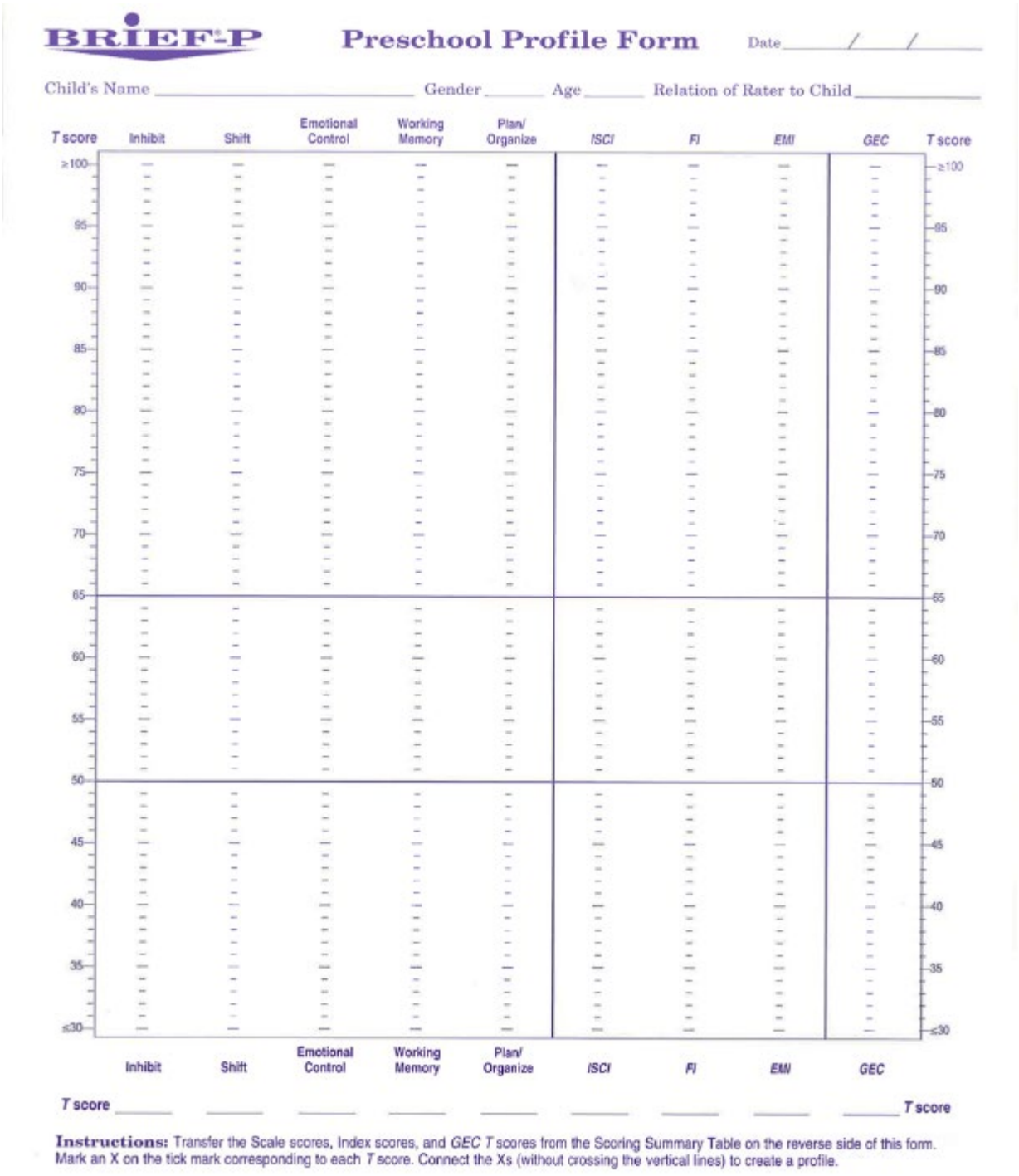
BRIEF-P
Preschool Profile Form
Date / /
Child's Name
Gender
Age
Relation of Rater to Child
T score
Inhibit
Shift
Emotional Control
Working Memory
Plan/ Organize
ISCI
FI
EMI
GEC
T score
≥100
95
90
85
80
75
70
65
60
55
50
45
40
35
≤30
Instructions: Transfer the Scale scores, Index scores, and GEC T scores from the Scoring Summary Table on the reverse side of this form. Mark an X on the tick mark corresponding to each T score. Connect the Xs (without crossing the vertical lines) to create a profile.

BRIEF®
Behavior Rating Inventory of Executive Function®
PARENT FORM

Gerard A. Gioia, PhD, Peter K. Isquith, PhD, Steven C. Guy, PhD, and Lauren Kenworthy, PhD

Instructions

On the following pages is a list of statements that describe children. We would like to know if your child has had problems with these behaviors over the past 6 months. Please answer all the items the best that you can. Please DO NOT SKIP ANY ITEMS. Think about your child as you read each statement and circle your response:

N	if the behavior is	**Never** a problem
S	if the behavior is	**Sometimes** a problem
O	if the behavior is	**Often** a problem

For example, if your child **never** has trouble completing homework on time, you would circle **N** for this item:

Has trouble completing homework on time (N) S O

If you make a mistake or want to change your answer, DO NOT ERASE. Draw an "X" through the answer you want to change, and then circle the correct answer:

Has trouble completing homework on time (X) (S) O

Before you begin answering the items, please fill in your child's name, gender, grade, age, birth date, your name, your relationship to the child, and today's date in the spaces provided at the top of the next page.

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Child's Name _____ Gender _____ Grade _____ Age _____ Birth Date ___/___/___

Your Name _____ Relationship to Child _____ Today's Date ___/___/___

N = Never S = Sometimes O = Often

1.	Overreacts to small problems	N	S	O
2.	When given three things to do, remembers only the first or last	N	S	O
3.	Is not a self-starter	N	S	O
4.	Leaves playroom a mess	N	S	O
5.	Resists or has trouble accepting a different way to solve a problem with schoolwork, friends, chores, etc.	N	S	O
6.	Becomes upset with new situations	N	S	O
7.	Has explosive, angry outbursts	N	S	O
8.	Tries the same approach to a problem over and over even when it does not work	N	S	O
9.	Has a short attention span	N	S	O
10.	Needs to be told to begin a task even when willing	N	S	O
11.	Does not bring home homework, assignment sheets, materials, etc.	N	S	O
12.	Acts upset by a change in plans	N	S	O
13.	Is disturbed by change of teacher or class	N	S	O
14.	Does not check work for mistakes	N	S	O
15.	Has good ideas but cannot get them on paper	N	S	O
16.	Has trouble coming up with ideas for what to do in play or free time	N	S	O
17.	Has trouble concentrating on chores, schoolwork, etc.	N	S	O
18.	Does not connect doing tonight's homework with grades	N	S	O
19.	Is easily distracted by noises, activity, sights, etc.	N	S	O
20.	Becomes tearful easily	N	S	O
21.	Makes careless errors	N	S	O
22.	Forgets to hand in homework, even when completed	N	S	O
23.	Resists change of routine, foods, places, etc.	N	S	O
24.	Has trouble with chores or tasks that have more than one step	N	S	O
25.	Has outbursts for little reason	N	S	O
26.	Mood changes frequently	N	S	O
27.	Needs help from an adult to stay on task	N	S	O
28.	Gets caught up in details and misses the big picture	N	S	O
29.	Keeps room messy	N	S	O
30.	Has trouble getting used to new situations (classes, groups, friends)	N	S	O
31.	Has poor handwriting	N	S	O
32.	Forgets what he/she was doing	N	S	O
33.	When sent to get something, forgets what he/she is supposed to get	N	S	O
34.	Is unaware of how his/her behavior affects or bothers others	N	S	O
35.	Has good ideas but does not get job done (lacks follow-through)	N	S	O
36.	Becomes overwhelmed by large assignments	N	S	O
37.	Has trouble finishing tasks (chores, homework)	N	S	O
38.	Acts wilder or sillier than others in groups (birthday parties, recess)	N	S	O
39.	Thinks too much about the same topic	N	S	O
40.	Underestimates time needed to finish tasks	N	S	O
41.	Interrupts others	N	S	O
42.	Does not notice when his/her behavior causes negative reactions	N	S	O
43.	Gets out of seat at the wrong times	N	S	O
44.	Gets out of control more than friends	N	S	O

N = Never S = Sometimes O = Often

45.	Reacts more strongly to situations than other children	N	S	O
46.	Starts assignments or chores at the last minute	N	S	O
47.	Has trouble getting started on homework or chores	N	S	O
48.	Has trouble organizing activities with friends	N	S	O
49.	Blurts things out	N	S	O
50.	Mood is easily influenced by the situation	N	S	O
51.	Does not plan ahead for school assignments	N	S	O
52.	Has poor understanding of own strengths and weaknesses	N	S	O
53.	Written work is poorly organized	N	S	O
54.	Acts too wild or "out of control"	N	S	O
55.	Has trouble putting the brakes on his/her actions	N	S	O
56.	Gets in trouble if not supervised by an adult	N	S	O
57.	Has trouble remembering things, even for a few minutes	N	S	O
58.	Has trouble carrying out the actions needed to reach goals (saving money for special item, studying to get a good grade)	N	S	O
59.	Becomes too silly	N	S	O
60.	Work is sloppy	N	S	O
61.	Does not take initiative	N	S	O
62.	Angry or tearful outbursts are intense but end suddenly	N	S	O
63.	Does not realize that certain actions bother others	N	S	O
64.	Small events trigger big reactions	N	S	O
65.	Talks at the wrong time	N	S	O
66.	Complains there is nothing to do	N	S	O
67.	Cannot find things in room or school desk	N	S	O
68.	Leaves a trail of belongings wherever he/she goes	N	S	O
69.	Leaves messes that others have to clean up	N	S	O
70.	Becomes upset too easily	N	S	O
71.	Lies around the house a lot ("couch potato")	N	S	O
72.	Has a messy closet	N	S	O
73.	Has trouble waiting for turn	N	S	O
74.	Loses lunch box, lunch money, permission slips, homework, etc.	N	S	O
75.	Cannot find clothes, glasses, shoes, toys, books, pencils, etc.	N	S	O
76.	Tests poorly even when knows correct answers	N	S	O
77.	Does not finish long-term projects	N	S	O
78.	Has to be closely supervised	N	S	O
79.	Does not think before doing	N	S	O
80.	Has trouble moving from one activity to another	N	S	O
81.	Is fidgety	N	S	O
82.	Is impulsive	N	S	O
83.	Cannot stay on the same topic when talking	N	S	O
84.	Gets stuck on one topic or activity	N	S	O
85.	Says the same things over and over	N	S	O
86.	Has trouble getting through morning routine in getting ready for school	N	S	O

BRIEF® Parent Form Scoring Summary

Date ____/____/____
Rater's Name _____

Child's Name _____ Gender _____ Grade _____ Age _____

Scoring Instructions

1. Remove the perforated stub and detach the top part of the carbonless answer sheet to reveal the scoring sheet.
2. Transfer the circled item score for each item to the box provided in that item row.
3. Sum the item scores in each column and enter the subtotal in the box at the bottom of the column.
4. Transfer the scale subtotals for Items 1-44 to the appropriate box in the row for Subtotals at the bottom of the facing page.
5. Sum the two Subtotals for each scale and enter the total in the Total Scale raw scores box beneath the scale name.
6. Transfer the Total raw score for each scale to the Raw score column in the Scoring Summary Table below.
7. Sum the raw scores for Inhibit, Shift, and Emotional Control to obtain the raw score for the Behavioral Regulation Index (*BRI*).
8. Sum the raw scores for Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor to obtain the raw score for the Metacognition Index (*MI*).
9. Sum the raw scores for the two indexes (*BRI* and *MI*) to obtain the raw score for the Global Executive Composite (*GEC*).
10. Locate the appropriate normative comparison group in the Appendix tables of the BRIEF Professional Manual. Find the raw score for each scale, index, or *GEC* in the raw score column, then move across the row to the corresponding *T* score and percentile. Enter the *T* score and percentile in the appropriate boxes in the Scoring Summary Table. Locate the Confidence Interval (CI) value for each scale, index, and *GEC* at the bottom of the appropriate column, calculate the high end (add the CI value to the *T* score) and low end (subtract the CI value from the *T* score) of the interval, and enter in the spaces provided under the heading 90% CI.

Scoring Summary Table

Scale/Index	Raw score	*T* score	%ile	90% CI
Inhibit				____ – ____
Shift				____ – ____
Emotional Control				____ – ____
BRI				____ – ____
Initiate				____ – ____
Working Memory				____ – ____
Plan/Organize				____ – ____
Organization of Materials				____ – ____
Monitor				____ – ____
MI				____ – ____
GEC (BRI + MI)				____ – ____

Negativity Scale

1. Locate the first Negativity item (indicated with a boxed **N** in the margin of the Scoring Sheet). For each Negativity item with a score of 3, circle that item number in the column to the right.
2. Count the number of circled items to determine the **Negativity score.**
3. Circle the appropriate Protocol classification based on that score.

Negativity score	Cumulative percentile	Protocol classification
≤4	≤90	Acceptable
5 to 6	91 – 98	Elevated
≥7	>98	Highly elevated

Item no.
8.
13.
23.
30.
62.
71.
80.
83.
85.

Negativity score (Range = 0 to 9)

Inconsistency Scale

For each item pair:

1. Transfer the item score for each item (marked (I) in the margin of the Scoring Sheet) to the appropriate item pairs box.
2. Subtract the *lesser* number from the *greater* number and enter the result in the *Difference* column.
3. Sum the numbers in the *Difference* column to obtain the **Inconsistency score.**
4. Circle the appropriate Protocol classification based on that score:

Inconsistency score	Cumulative percentile	Protocol classification
≤6	≤98	Acceptable
7 to 8	99	Questionable
≥9	>99	Inconsistent

Item no.	Score	Item no.	Score		Difference
7.		25.		→	
11.		22.		→	
27.		17.		→	
33.		32.		→	
38.		59.		→	
41.		65.		→	
42.		63.		→	
44.		54.		→	
53.		60.		→	
55.		44.		→	

Inconsistency score (Range = 0 to 20)

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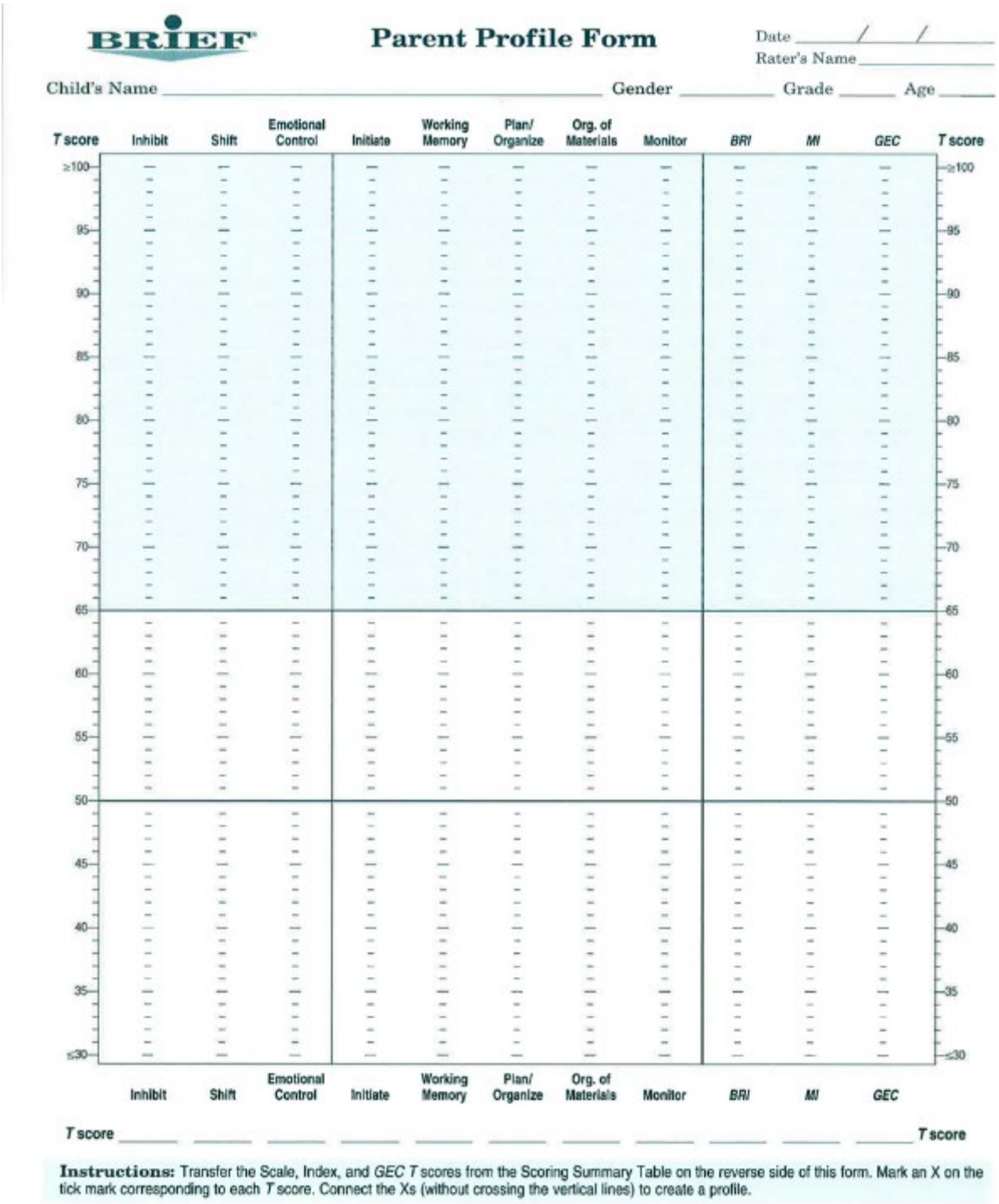


BRIEF

Parent Profile Form

Date ____/____/____

Rater's Name _____

Child's Name _____ Gender _____ Grade _____ Age _____

T score	Inhibit	Shift	Emotional Control	Initiate	Working Memory	Plan/ Organize	Org. of Materials	Monitor	BRI	MI	GEC	T score
≥100												≥100
95												95
90												90
85												85
80												80
75												75
70												70
65												65
60												60
55												55
50												50
45												45
40												40
35												35
≤30												≤30
	Inhibit	Shift	Emotional Control	Initiate	Working Memory	Plan/ Organize	Org. of Materials	Monitor	BRI	MI	GEC	
T score												T score

Instructions: Transfer the Scale, Index, and *GEC T* scores from the Scoring Summary Table on the reverse side of this form. Mark an X on the tick mark corresponding to each *T* score. Connect the Xs (without crossing the vertical lines) to create a profile.

APPENDIX 4 – VINELAND ADAPTIVE BEHAVIOR SCALE

Communication

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know

Listening and Understanding

						Circle "?" If You Have a Question
Start Age 0–4	1	Turns eyes and head toward sound.	2	1	0	?
	2	Looks toward parent or caregiver when hearing parent's or caregiver's voice.		1	0	?
	3	Responds to his or her name spoken (for example, turns toward speaker, smiles, etc.).	2		0	?
	4	Demonstrates understanding of the meaning of *no*, or word or gesture with the same meaning (for example, stops current activity, smiles, etc.).			0	?
	6	Listens to story for at least 5 minutes (that is, remains relatively still and directs attention to the storyteller or reader).	2	1	0	?
	5	Demonstrates understanding of the meaning of *yes*, or word or gesture with the same meaning (for example, continues activity, smiles, etc.).	2	1	0	?
	7	Points to at least three major body parts when asked (for example, nose, mouth, hands, feet, etc.).	2	1		?
Start Age 5+	8	Points to common objects in a book or magazine as they are named, (for example, dog, car, up, key, etc.).	2	1	0	?
	9	Listens to instructions.	2	1		?
	10	Follows instructions with one action and one object (for example, "Bring me the book"; "Close the door"; etc.).	2	1		?
	11	Points to at least five minor body parts when asked (for example, fingers, elbows, teeth, toes, etc.).	2	1		?
	12	Follows instructions with two actions or an action and two objects (for example, "Bring me the crayons and the paper"; "Sit down and eat your lunch"; etc.).	2	1	0	?
	13	Follows instructions in "if-then" form (for example, "If you want to play outside, then put your things away"; etc.).	2			?
	14	Listens to a story for at least 15 minutes.	2	1	0	?
	15	Listens to a story for at least 30 minutes.	2	1	0	
	16	Follows three-part instructions (for example, "Brush your teeth, get dressed, and make your bed"; etc.).	2	1	0	
	17	Follows instructions or directions heard 5 minutes before.		1	0	1
	18	Understands sayings that are not meant to be taken word for word (for example, "Button your lip"; "Hit the road"; etc.).	2		0	?
	19	Listens to an informational talk for at least 15 minutes.	2	1	0	?
	20	Listens to an informational talk for at least 30 minutes.	2			?

Talking

						Circle "?" If You Have a Question
Start Age 0–4	1	Cries or fusses when hungry or wet.	2			1
	2	Smiles when you smile at him or her.	2	1	0	?
	3	Makes sounds of pleasure (for example, coos, laughs, etc.).	2	1	0	1
	4	Makes nonword baby sounds (that is, babbles).	2	1	0	?
	5	Makes sounds or gestures (for example, waves arms) to get parent's or caregiver's attention.	2	1	0	?
	6	Makes sounds or gestures (for example, shakes head) if he or she wants an activity to stop or keep going.	2	1	0	?

Communication, continued

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know

Talking, *continued*

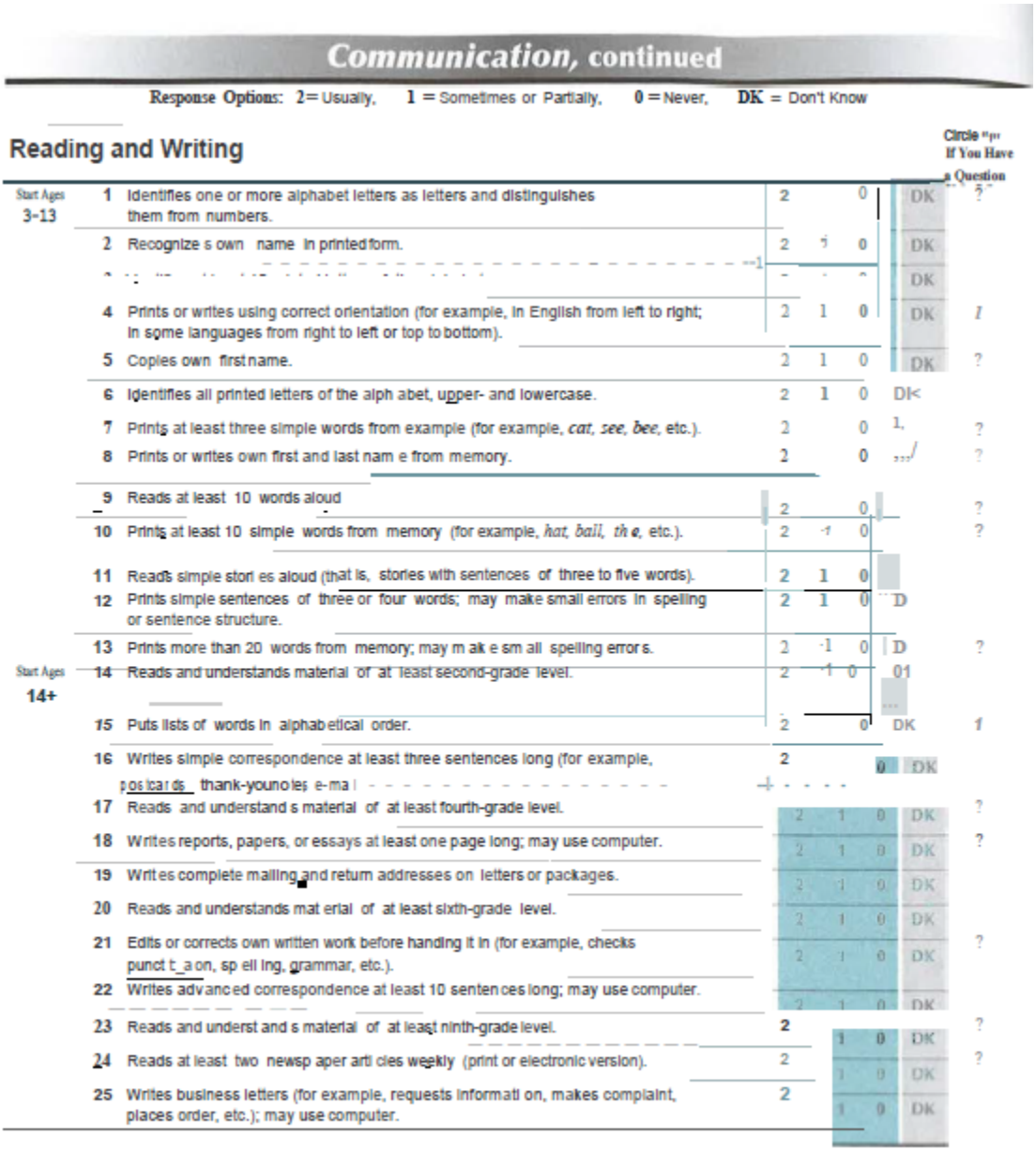
						Circle "?" If You Have a Question
	7	Waves good-bye when another person waves or parent or caregiver tells him or her to wave.	2	1	0	DK	?
	8	Says "Da-da," "Ma-ma," or another name for parent or caregiver (including p e 's regiver's first name or nickname).	2		0	DK	
	9	Points to object he or she wants that is out of reach.	2	1	0	DK	
	10	Points or gestures to indicate preference when offered a choice (for example, " Dp you want this one or that one?"; etc.).	2	1	0	DK	?
	11	Repeats or tries to repeat common words immedi ate ly upon hearing them (for example, *ball, car,* go, etc.).	2	1		DK	
	12	Names at least three objects (for example, bottle, dog, favorite toy, etc.).	2	1	ti	DK	
	13	Says one-word requests (for example, *up, more, out,* etc.).	'2	1	0	DK	?
	14	Uses first names or nicknames of brothers, sisters, or friends, or ays their names when asked.	2	1	fl	DK	?
	15	Answers or tries to answer with words when asked a que stion.	2	1	0	DK	
	16	Names at least 10 objects.	2	1	0	DK	?
	17	States own first name or nickname (for example, Latesha, Little Sister, etc.) when asked.	2	1	0	DK	?
	18	Uses phrases with a noun and a verb (for example, "Katie stay"; "Go home"; etc.).	2	1	0	DK	?
	19	Asks questions by changing inflection of words or simple phrases ("M i ne ; "Me go?"; etc.); grammar is not important.	2	1	0	DK	
	20	Says at least 50 recognizable words.	2	1	0	DK	*l*
	21	Uses simple words to describe things (for example, *dirty, pretty, big, loud,* etc.).	2	1	0	DK	?
	22	Asks questions beginning with *what* or *where* (for example, "What's that?"; "Where dog ie go?" ; etc.).	2	1	0	DK	?
	23	Uses negatives in sentences (for example, "Me no go"; "I won't drink it"; etc.); grammar is not important.	2	1	0	DK	?
	24	Tells about experiences in simple sentences (for example, "Ginger and I play"; "Dan read me a book"; etc.).	2	1	0	DK	?
Start Ages 5–13	25	Says correct age when asked.	2	1	0	DK	?
	26	Says at least 100 recognizable words.	2	1	0	DK	?
	27	Uses *in, on,* or *under* in phrases or sentences (for example, "Ball go under chair"; "Put it on the table"; etc.).	2	1	-0	DK	?
	28	Uses *and* in phrases or sentences (for example, "M om and Dad"; "I want ice cream and cake"; etc.).	2	1	0	DK	?
	29	Says first and last name when asked.	2	1		DK	?
	30	Identifies and names mo t common colors (that is, red, blue, green, yellow, orange, purple , bro wn, and black). Recording: Mark "2" if the individual names 6 to 8 colors; mark "1" if the individual n mes 2 to 5 colors; mark "0" if the individual names 0 or 1 color.	2	1	0	OK	?
	31	Asks questions beginning with *who* or *why* (for example, "Who's that?"; "Why do I have to go?"; etc.).	2	1	0	DK	?
	32	Uses present tense verbs ending in *ing* (for example, "Is singing"; "Is playing"; etc.).	2	1	0	DK	?

Communication, continued

Response Options: **2** = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Do n't Know

Talking, *continued*

						Circle "I" If You Have a Question
	33	Uses possessives in phrases or sentences (for example, "That\ her book"; "This is Carlos's ball"; etc.).	2	1	0	DK	?
	34	Uses pronouns in phrases or sentences; must use correct gender and form of the pronoun, but sentences need not be grammatically correct (for example, "H done it"; "They went"; etc.).	2	1	0	DK	
	35	Asks questions beginning with *when* (for example, "When is dinner?"; "W hen can we go home?"; etc.).	2	1	0	DK	?
	36	Uses regular past tense verbs (for example , *walked, baked,* etc.); may use irregular past tense verbs ungrammatically (for exampl "I runned away"; etc.).	2	1	0	DK	?
	37	Uses *behind* or *in front of* in phrases or sentences (for exampl e, "I walked in front of her"; "Terrell is behind you"; etc.).	2	1	0	DK	?
	38	Pronounces words clearly without sound substitutions (for examp le, does not say "wab bit" for "rabbit," "Thally" for "Sally," etc.).	2	1	0	DK	?
	39	Tells basic parts of a story, fairy tale, or televisio n show plot; does not need to include great detail or reco unt in perfect order.	2	1	0	DK	?
Start Ages 14+	40	Says month and day of birthday when asked.	2	1	0	DK	
	41	Modulates tone of voice, volume, and rhythm appropriately (for example, does not consistently speak too loudly, too softly, or in a monotone, etc.).	2	1	0	DK	?
	42	Tells about experiences in detail (for exampl e, tells who was involved, where activity took place, etc.).	2	1	0	DK	
	43	Gives simple directions (for example, on how to play a game or how to make something). COfih6"flp; Mark "2" if the directions are clear enough to follow; mark "1" if the individual articulates directions but they are not clear enough to follow; mark "O" if the individual never attempts to articulate directions.	2	1	0		?
	44	Uses *between* in phrases or sentences (for example, "The ball went between the cars; etc.).	2		0		?
	45	Says own telephone number when asked.	2	1	0	DK	?
	46	Easily moves from one topic to another in conversation.	2	1	0	DK	?
	47	Stays on topic in conversations; does not go off on tangent s.	2	1	0	DK	?
	48	Explains ideas in more than one way (for example, "This was a good book. It was exciting and fun to read"; etc.)	2	1	0	DK	?
	49	Has conversations that last 10 minutes (for example, relates experiences, contributes ideas, shares feelings, etc.).	2	1	0	DK	?
	50	Uses irregular plurals correctly (for example, *childre n, geese,* mice, *women,* etc.).	2	1	0	DK	?
	51	Says complete home address (that is, street or rural route, apartment number, city, and state), with or without zip code, when asked.	2	1	0	DK	?
	52	Describes a short-term goal and what he or she needs to do to reach it (for example, says, " I want to get an A on my test, so I' m going to st y ard"; etc.).	2	1	0	DK	?
	53	Gives complex directions to others (for example, to a distant location, for recipe with many ingredients or steps, etc.). rl ,oTJ Mark "2" if the directions are clear enough to follow; mark "1" if the to t> p: individual articulates directions but they are not clear enough to follow; mark "O" if the individual never attempts to articu late directions.	2	1	0	DK	?
	54	Describes a realistic long-range goal that can be done in 6 months or more (for example, says, "I want to buy a bike, so I' ll babysit and run errands to earn enough money to buy it"; etc.).	2	1	0	DK	?



Communication, continued

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know

Reading and Writing

						Circle "p" If You Have a Question
Start Ages 3–13	1	Identifies one or more alphabet letters as letters and distinguishes them from numbers.	2		0	DK ?
	2	Recognizes own name in printed form.	2	1	0	DK
						DK
	4	Prints or writes using correct orientation (for example, in English from left to right; in some languages from right to left or top to bottom).	2	1	0	DK I
	5	Copies own first name.	2	1	0	DK ?
	6	Identifies all printed letters of the alphabet, upper- and lowercase.	2	1	0	DK
	7	Prints at least three simple words from example (for example, *cat, see, bee,* etc.).	2		0	1, ?
	8	Prints or writes own first and last name from memory.	2		0	?
	9	Reads at least 10 words aloud	2		0	?
	10	Prints at least 10 simple words from memory (for example, *hat, ball, the,* etc.).	2	1	0	?
	11	Reads simple stories aloud (that is, stories with sentences of three to five words).	2	1	0	
	12	Prints simple sentences of three or four words; may make small errors in spelling or sentence structure.	2	1	0	D
	13	Prints more than 20 words from memory; may make small spelling errors.	2	1	0	D ?
Start Ages 14+	14	Reads and understands material of at least second-grade level.	2	1	0	01
	15	Puts lists of words in alphabetical order.	2		0	DK I
	16	Writes simple correspondence at least three sentences long (for example, postcards, thank-you notes, e-mail)	2		0	DK
	17	Reads and understands material of at least fourth-grade level.	2	1	0	DK ?
	18	Writes reports, papers, or essays at least one page long; may use computer.	2	1	0	DK ?
	19	Writes complete mailing and return addresses on letters or packages.	2	1	0	DK
	20	Reads and understands material of at least sixth-grade level.	2	1	0	DK
	21	Edits or corrects own written work before handing it in (for example, checks punctuation, spelling, grammar, etc.).	2	1	0	DK ?
	22	Writes advanced correspondence at least 10 sentences long; may use computer.	2	1	0	DK
	23	Reads and understands material of at least ninth-grade level.	2	1	0	DK ?
	24	Reads at least two newspaper articles weekly (print or electronic version).	2	1	0	DK ?
	25	Writes business letters (for example, requests information, makes complaint, places order, etc.); may use computer.	2	1	0	DK

Caring for Self

							Circle "?" If You Have a Question
Start Ages 0-8	1	Opens mouth when food is offered.	2		0	DK	?
	2	Eats solid foods (for example, cooked vegetables, chopped meats, etc.).	2	1	0	DK	?
	3	Sucks or chews on finger foods (for example, crackers, cookies, toast, etc.).	2	1	0	DK	?
	4	Drinks from a cup or glass; may spill.	2	1	0	DK	?
	5	Lets someone know when he or she has wet or soiled diaper or pants (for example, points, vocalizes, pulls at diaper, etc.).	2	1	0	DK	?
	6	Feeds self with spoon; may spill.	2	1	0	DK	?
	7	Sucks from straw.	2	1	0	DK	?
	8	Takes off clothing that opens in the front (for example, a coat or sweater); does not have to unbutton or unzip the clothing.	2	1	0	DK	?
	9	Pulls up clothing with elastic waistbands (for example, underwear or sweatpants).	2	1	0	DK	?
	10	Feeds self with fork; may spill.	2	1	0	DK	?
	11	Drinks from a cup or glass without spilling.	2	1	0	DK	?
	12	Feeds self with spoon without spilling.	2	1	0	DK	?
	13	Urinates in toilet or potty chair.	2	1	0	DK	?
	14	Puts on clothing that opens in the front (for example, a coat or sweater); does not have to zip or button the clothing.	2	1	0	DK	?
	15	Asks to use toilet.	2	1	0	DK	?
	16	Defecates in toilet or potty chair.	2	1	0	DK	?
	17	Is toilet-trained during the day.	2	1	0	DK	?
		r:Ing'Op: Mark "2" if the individual uses the toilet without help and without accidents; mark "1" if the individual needs help, such as with wiping, or has some accidents; the individual always needs help or has frequent accidents.					
	18	Zips zippers that are fastened at the bottom (for example, in pants, on backpacks, etc.).	2	1	0	DK	?
	19	Wipes or blows nose using tissue or handkerchief.	2	1	0	DK	?
	20	Is toilet-trained during the night.		1	0	DK	?
	21	Puts shoes on correct feet; does not need to tie laces.	2	1	0	DK	?
	22	Fastens snaps.	2	1	0	DK	?
Start Ages 9+	23	Holds spoon, fork, and knife correctly.	2	1	0	DK	?
	24	Washes and dries face using soap and water.	2	1	0	DK	?
	25	Brushes teeth. nirnti Tiri: Mark "2" if the individual brushes teeth without help, including putting toothpaste on the brush, and without being told to brush; mark "1" if the individual needs help brushing or putting toothpaste on the brush or needs frequent reminders; mark "0" if the individual never brushes without help or without being reminded.	2	1	0	DK	?
	26	Buttons large buttons in front, in correct buttonholes.	2	1	0	DK	?
	27	Covers mouth and nose when coughing and sneezing.	2	1	0	DK	?

Daily Living, continued

Response Options: 2 = Usually, **1** = Sometimes or Partially, **0** = Never, **DK** = Don't Know **N/0** = No Opportunity

Caring for Self, *continued*

						Circle "?" If You Have a Question
28	Buttons small buttons in front, in correct buttonholes.	2		0	DK	?
29	Connects and zips zippers that are not fastened at the bottom (for example, in jackets, sweaters, t-shirts, etc.).	2		0	DK	?
30	Turns faucets on and adjusts temperature by adding hot or cold water.	2		0	DK	?
31	Wears appropriate clothing during wet or cold weather (for example, raincoat, boots, sweater, etc.).	2		0	DK	?
32	Bathes or showers and dries self.	2		0	DK	
	Scoring Tip: Mark "2" if the individual bathes or showers without help, including turning the water on and off; mark "1" if the individual needs help with any part of bathing or drying or with turning the water on and off; mark "0" if the individual never bathes or showers without help or without reminders.					
33	Finds and uses appropriate public restroom for his or her gender.	2		0	DK	?
34	Washes and dries hair (with towel or hair dryer).	2		0	DK	?
35	Cares for minor cuts (for example, cleans wound, puts on bandage, etc.).	2		0	DK	?
36	Takes medicine as directed (that is, follows directions on label).	2		0	DK	?
37	Uses thermometer to take own or another's temperature.	2		0	DK	?
38	Seeks medical help in an emergency (for example, recognizes symptoms of serious illness or injury, such as shortness of breath, chest pain, uncontrolled bleeding, etc.).	2		U	DK	?
	Scoring Tip: You may mark "N/O" for No Opportunity if the individual has not been in a medical emergency.			N/0		
39	Follows directions for health care procedures, special diet, or medical treatments.	2	1	0	DK	
	Scoring Tip: You may mark "N/0" for No Opportunity if the individual does not have a health concern that requires special procedures, diet, or treatments.			N/0		
40	Keeps track of medications (nonprescription and prescription) and refills them as needed.	2	1	0	DK	?
41	Makes appointments for regular medical and dental checkups.	2		0	DK	?

Caring for Home

						Circle "?" If You Have a Question
Start Ages 1-13	1 Is careful around hot objects (for example, the stove or oven, an open fire, etc.).	2		0	DK	
	2 Helps with simple household chores (for example, dusts, picks up clothes or toys, feeds pet, etc.).			0	DK	?
	3 Clears unbreakable items from own plate/table.			0	DK	?
	4 Cleans up play or work area at end of an activity (for example, finger painting, model building, etc.).	2		0	DK	?
	5 Puts away personal possessions (for example, toys, books, magazines, etc.).	2		0	DK	?
	6 Is careful when using sharp objects (for example, scissors, knives, etc.).	2		0	DK	?
Start Ages 14+	7 Clears breakable items from own place at table.			0	DK	?
	8 Helps prepare foods that require mixing and cooking (for example, cake or cookie mixes, macaroni and cheese, etc.).	2		0	DK	?
	9 Uses simple appliances (for example, a toaster, can opener, bottle opener, etc.).	2		0	DK	?

Daily Living, continued

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know N/0 = No Opportunity

Caring for Home, *continued*

						Circle "?" If You Have a Question
10	Uses microwave oven for heating, baking, or cooking (th at is, sets time and power setting, etc.). Scoring Tip: You may mark "N/0" for No Opportunity if there is no microwave in the home.	2	1	0	DK / N/0	?
11	Puts clean clothes away in prop er place (for exampl e, in drawers or cl oset, on hooks, etc.).	2	1	0	DK	?
12	Uses tools (for example, a hammer to driv e nails, a screwdriver to screw and unscrew screws, etc.).	2		0	DK	?
13	Washes dishes by hand, or loads and uses dishwasher.	2		0	DK	?
14	Sweeps, mops, or vacuums floors thoroughly. Scoring Tip: Mark "2" if the individual mops, sweeps, or vacuums so well that the task does not have to redone; mark "1" if the individual doesn't consistently complete the task well; mark "0" if the individual never mops, sweeps, or vacuums, or does the task so poorly that it always needs to be redone.	2		0	DK	?
15	Clears table completely (for example, scrapes and stacks dish es, throws away disposabl e items, etc.).	2		0	DK	
16	Uses household products correctly (for example, laundry detergent, furniture polish, glass cleaner, etc.).	2	1	0	DK	?
17	Prepares basic foods that do not need mixing but require cooking (for example, rice, soup, vegetables, etc.).	2		0	DK	?
18	Cleans one or more rooms other than own bedroom.	2		0	DK	?
19	Uses sharp knife to prepare food.	2		0	DK	
20	Uses stove or oven for heating, baking, or cooking (that is, turns burners on and off, sets oven temperature, etc.).	2		0	DK	?
21	Prepares food from ingredients that require measuring, mixing, and cooking.	2	1	0	DK	?
22	Washes clothing as needed.		1	0	DK	?
23	Performs maintenance tasks as needed (for example, replaces light bulbs, hanges vacuum l an r bag, e	2		0	DK	?
24	Plans and prepares main meal of the day.			0	DK	

Living in the Community

						Circle "?" If You Have a Question
Start Ages 1–9	1	D emon strates understanding of function of telephone (for exampl e, pretends to talk on phone, etc.).	2		0	DK	?
	2	Talks to familiar person on telephone.	2	1	0	DK	
	3	Uses TV or radio without help (for example, turns equipm ent on, accesses channel or station, selects program, etc.). Scoring Tip: You may mark "N/O" for No Opportunity if there is no TV or radio in the home.	2	1	0	DK / N/0	
	4	Counts at least 10 objects, one by one.	2		0	DK	?
	5	Is aware of and demonstrates appropriate behavior while riding in car (for example, keeps seat belt on, refrains from distracting driver, etc.).	2	1	0	DK	?
	6	Demonstrates understanding of the function of money (for example, says, "Money is what you need to buy things at the st ore"; etc.).	2	1	0		
	7	Uses sidewalk (where available) or shoulder of road when walking or using wheeled equipment (skates, scooter, tri cyc etc.).		1	0		

Daily Living, continued

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know N/0 = No Opportunity

Living in the Community, *continued*

						Circle "?" If You Have a Question
	8	Demonstrates understanding of function of clock (for example, says, "Clocks tell time"; "What time can we go?"; etc.).	2	1	0	DK	?
	9	Follows household rules (for example, no running in the house, no jumping on the furniture, etc.).	2	1	0	DK	?
	10	Demonstrates computer skills necessary to play games or start programs with computer turned on; does not need to turn computer on by self. Scoring Tip: You may mark "N/0" for No Opportunity if there is no computer in the home.	2	1	/0		?
	11	Summons to the telephone the person receiving a call or indicates that the person is not available.	2	1	0	DK	?
Start Ages 10-15	12	Identifies penny, nickel, dime, and quarter by name when asked; does not need to know the value of coins.	2	1	0	DK	?
	13	Looks both ways when crossing streets or roads.	2	1	0	DK	?
	14	Says current day of the week when asked.	2	1	0	DK	?
	15	Demonstrates understanding of right to personal privacy for self and others (for example, while using restroom or changing clothes, etc.).	2	1	0	DK	?
	16	Demonstrates knowledge of what phone number to call in an emergency when asked.	2				?
	17	Tells time using a digital clock or watch.	2				?
	18	States value of penny (1 cent), nickel (5 cents), dime (10 cents), and quarter (25 cents).	2				?
	19	Discriminates between bills of different denominations (for example, refers to $1 bills, $5 bills, etc., in conversation; etc.).	2				?
	20	Obeys traffic lights and *Walk* and *Don't Walk* signs.	2	1		DK	?
	21	Points to current or other date on calendar when asked.	2	1	0	DK	?
	22	Demonstrates understanding that some items cost more than others (for example, says, "I have enough money to buy gum but not a candy bar"; "Which pencil costs less?"; etc.).	2	1	0	DK	?
Start Ages 16+	23	Tells time by the half hour on analog clock (for example, 1:30, 2:00, etc.).	2	1	0	DK	?
	24	Makes telephone calls to others, using standard or cell phone.	2	1	0	DK	?
	25	Orders a complete meal in a fast-food restaurant. Scoring Tip: You may mark "N/0" for No Opportunity if the individual has never eaten at a fast-food restaurant.	2	1	0 N/0	DK	?
	26	Carries or stores money safely (for example, in wallet, purse, money belt, etc.).	2	1	0	DK	?
	27	Tells time by 5-minute segments on analog clock (for example, 1:05, 1:10, etc.).	2	1	0	DK	?
	28	Obeys curfew parent or caregiver sets.	2	1	0	DK	?
	29	Watches or listens to programs for information (for example, weather report, news, educational program, etc.). Scoring Tip: You may mark "N/0" for No Opportunity if there is no TV or radio in the home.	2	1	0 N/0	DK	?
	30	Counts change from a purchase.	2			DK	?
	31	Demonstrates computer skills necessary to carry out complex tasks (for example, word processing, accessing the Internet, installing software, etc.). Scoring Tip: You may mark "N/0" for No Opportunity if there is no computer in the home.	2		N/0	DK	?
	32	Evaluates quality and price when selecting items to purchase.	2	1	0	DK	?
	33	Obeys time limits for breaks (for example, lunch or coffee breaks, etc.).	2	1	0	DK	?

Daily Living, continued

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know N/0 = No Opportunity

Living in the Community, *continued*					Circle "?" If You Have a Question
34 Travels at least 5 to 10 miles to familiar destination (that is, bikes, uses public transportation, or drives self).	2	1			?
35 Demonstrates understanding of right to complain or report legitimate problems when dissatisfied with services or situations.	2	1			?
36 Notifies school or supervisor when he or she will be late or absent.	2				?
37 Uses savings or checking account responsibly (for example, keeps some money in account , tracks balance carefully, etc.).	2	1			?
38 Travels at least 5 to 10 miles to unfamiliar destination (that is, bikes, uses public transpo rtation, or drives self).	2				?
39 Earns money at part-time job (that is, at least 10 hours a week) for 1 year. rlflSTip Do not mark 1.	2	:>(			?
40 Attempts to improve job performance after receiving constructive criticism from supervisor. rJns Tip: You may mark " N/0 " for No Opportunity if the individu al has not "!> • held a job.	2	1			?
41 Manages own money (for example, pays most or all own expenses, uses checks or money orders for purchases as needed, etc.).	2	1	0	DK	
42 Has held full-time job for 1 year. $:00 Till): Do not mark 1.	2	X	0	DK	?
43 Budgets for monthly expenses (for example, utilities, rent, etc.).	2	1	0	DK	*1*
44 Applies for and uses personal credit card responsibly (for example, does not exceed credit limit, pays on time, etc.).	2		0	DK	?

Social Skills and Relationships

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know

Relating to Others

						Circle "?" If You Have a Question
Start Ages 0-4		Looks at face of parent or caregiver.	2	1	0	DK	
	2	Watches (that is, follows with eyes) someone moving by crib or bed for 5 seconds or more.	2	1	0	DK	?
	3	Shows two or more emotions (for example, laughs, cries, screams, etc.).	2	1	0	DK	?
	4	Smiles or makes sounds when approached by a familiar person.	2	1	0	DK	?
	5	Makes or tries to make social contact (for example, smiles, makes noises, etc.).	2	1	0	DK	?
	6	Reaches for familiar person when person holds out arms to him or her.	2	1	0	DK	?
	7	Shows preference for certain people and objects (for example, smiles, reaches for or moves toward person or object, etc.).	2	1	0	DK	?
	8	Shows affection to familiar persons (for example, touches, hugs, kisses, cuddles, etc.).	2	1	0	DK	
	9	Imitates or tries to imitate parent's or caregiver's facial expressions (for example, smiles, frowns, etc.).	2	1	0	DK	?
	10	Moves about looking for parent or caregiver or other familiar person nearby.	2	1	0	DK	?
	11	Shows interest in children the same age, other than brothers or sisters (for example, watches them, smiles at them, etc.).	2	1	0	DK	?
Start Ages 5-15	12	Imitates simple movements (for example, claps hands, waves good-bye, etc.).	2	1	0	DK	?
	13	Uses actions to show happiness or concern for others (for example, hugs, pats arm, holds hands, etc.).	2	1	0	DK	?
	14	Shows desire to please others (for example, shares a snack or toy, tries to help even if not capable, etc.).	2	1	0	DK	?
	15	Demonstrates friendship-seeking behavior with others the same age (for example, says, "Do you want to play?" or takes another child by the hand, etc.).	2	1	0	DK	?
	16	Imitates relatively complex actions as they are being performed by another person (for example, shaving, putting on makeup, hammering nails, etc.).	2	1	0	DK	?
	17	Answers when familiar adults make small talk (for example, if asked, "How are you?" says, "I'm fine"; if told, "You look nice," says, "Thank you"; etc.).	2	1	0	DK	?
	18	Repeats phrases heard spoken before by an adult (for example, "Honey, I'm home"; "No de you clean your plate"; etc.).	2	1	0	DK	?
	19	Uses words to express own emotions (for example, "I'm happy"; "I'm scared"; etc.).	2	1	0	DK	?
	20	Has best friend or shows preference for certain friends (of either sex) over others.	2	1	0	DK	?
	21	Imitates relatively complex actions several hours after watching someone else perform them (for example, shaving, putting on makeup, hammering nails, etc.).	2	1	0	DK	?
Start Ages 16+	22	Uses words to express happiness or concern for others (for example, says, "Yeah! You won"; "Are you all right?"; etc.).	2	1	0	DK	?
	23	Acts when another person needs a helping hand (for example, holds door open, picks up dropped items, etc.).	2	1	0	DK	?
	24	Recognizes the likes and dislikes of others (for example, says, "Chow likes soccer"; "Susie doesn't eat pizza"; etc.).	2	1	0	DK	?
	25	Shows same level of emotion as others around him or her (for example, does not downplay or overdramatize a situation, etc.).	2	1	0	DK	?
	26	Keeps comfortable distance between self and others in social situations (for example, does not get too close to another person when talking, etc.).	2	1	0	DK	?

Social Skills and Relationships continued

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know

Relating to Others, *continued*

						Circle "?" If You Have a Question
27	Talks with others about shared interests (for example, sports, TV shows, summer plans, etc.).	2	1	0	DK	?
28	Starts small talk when meets people he or she knows (for example, says, "How are you?"; "What's up?"; etc.).	2	1	0	DK	?
29	Meets with friends regularly.	2	1	0	DK	?
30	Chooses not to say embarrassing or mean things or ask rude questions in public.	2	1	0	DK	?
31	Places reasonable demands on friendship (for example, does not expect to be a person's only friend or to have the friend always available, e	2		0	DK	?
32	Understands that others do not know his or her thoughts unless he or she says them.	2	1	0	DK	?
33	Is careful when talking about personal things.	2	1	0	DK	
34	Cooperates with others to plan or be part of an activity (for example, a birthday party, sports event, etc.).	2		0	DK	?
35	Demonstrates understanding of hints or indirect cues in conversation (for example, knows that yawns may mean, "I'm bored," or a quick change of subject may mean, "I don't want to talk about that"; etc.).	2	1	0	DK	?
36	Starts conversations by talking about things that interest others (for example, "Tyrone tells me you like computers"; etc.).	2		0	DK	?
37	Goes on group dates.	2	1	0	DK	?
38	Goes on single dates.	2		0	DK	?

Playing and Using Leisure Time

						Circle "?" If You Have a Question
Start Ages 0–7	1 Responds when parent or caregiver is playful (for example, smiles, laughs, claps hands, etc.).	2	1	0	DK	?
	2 Shows interest in where he or she is (for example, looks or moves around, touches objects or people, etc.).	2		0	DK	?
	3 Plays simple interaction games with others (for example, peekaboo, patty-cake, etc.).	2	1	0	DK	?
	4 Plays near another child, each doing different things.	2		0	DK	?
	5 Chooses to play with other children (for example, does not stay on the edge of a group or avoid others).	2		0	DK	?
	6 Plays cooperatively with one or more children for up to 5 minutes.	2		0	DK	
	7 Plays cooperatively with more than one child for more than 5 minutes.	2				?
	8 Continues playing with another child with little fussing when parent or caregiver leaves.	2				?
	9 Shares toys or possessions when asked.	2		0	DK	?
Start Ages 8–15	10 Plays with others with minimal supervision.	2		0	DK	?
	11 Uses common household objects or other objects for make-believe activities (for example, pretends a block is a car, a box is a house, etc.).	2	1	0	DK	?
	12 Protects self by moving away from those who destroy things or cause injury (for example, those who bite, hit, throw things, pull hair, etc.).	2	1	0	DK	?
	13 Plays simple make-believe activities with others (for example, plays dress-up, pretends to be superheroes, etc.).	2	1	0	DK	?

Social Skills and Relationships, continued

Response Options: 2 = Usually; **1 =** Sometimes or Partially, **0 =** Never, **DK** = Don't Know

Playing and Using Leisure Time, *continued*

						Circle "?" If You Have a Question
	14	Seeks out others for play or companionship (for example, invites others home, goes to another's home, plays with others on the playground, etc.).	2	1	0	DK	?
	15	Takes turns when asked while playing games or sports.	2	1	0	DK	?
	16	Plays in formal, outdoor group games (for example, tag, jump rope, catch, etc.).	2	1	0	DK	?
	17	Shares toys or possessions without being asked.	2	1	0	DK	?
	18	Follows rules in simple games (relay races, spelling bees, electronic games, etc.).	2	1	0	DK	?
	19	Takes turns without being asked.	2	1	0	DK	?
	20	Plays simple card or board game based only on chance (for example, Go Fish, Crazy Eights, Sorry™, etc.).	2	1	0	DK	?
	21	Goes places with friends during the day with adult supervision (for example, to a shopping mall, park, community center, etc.).	2	1	0	DK	?
Start Ages 16+	22	Asks permission before using objects belonging to or being used by another.	2	1	0	DK	?
	23	Refrains from entering group when nonverbal cues indicate that he or she is not welcome.	2	1	0	DK	?
	24	Plays simple games that require keeping score (for example, kickball, pickup basketball, etc.).	2	1	0	DK	?
	25	Shows good sportsmanship (that is, follows rules, is not overly aggressive, congratulates other team on winning, and does not get mad when losing).	2	1	0	DK	?
	26	Plays more than one board, card, or electronic game requiring skill and decision making (for example, Monopoly™, Cribbage, etc.).	2	1	0	DK	?
	27	Goes places with friends in evening with adult supervision (for example, to a concert, lecture, sporting event, movie, etc.).	2	1	0	DK	?
	28	Follows rules in complex games or sports (for example, football, soccer, volleyball, etc.).	2	1	0	DK	?
	29	Goes places with friends during the day without adult supervision (for example, to a shopping mall, park, community center, etc.).	2	1	0	DK	?
	30	Plans fun activities with more than two things to be arranged (for example, a trip to a beach or park that requires planning transportation, food, recreational items, etc.).	2	1	0	DK	?
	31	Goes places with friends in evening without adult supervision (for example, to a concert, lecture, sporting event, movie, etc.).	2	1	0	DK	?

Social Skills and Relationships, continued

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know

Adapting

							Circle "?" If You Have a Question
Start Ages 1+	1	Changes easily from one at-home activity to another.	2	1	0	DK	?
	2	Says "thank you" when given something.	2		0	DK	
	3	Changes behavior depending on how well he or she knows another person (for example, acts differently with family member than with stranger, etc.).	2	1	0	DK	?
	4	Chews with mouth closed.	2	1	0	DK	?
	5	Says "please" when asking for something.	2	1	0	DK	?
	6	Ends conversations appropriately (for example, says, "Good-bye"; "See you later"; etc.).	2	1	0	DK	?
	7	Cleans or wipes face and hands during and/or after meals.	2	1	0	DK	
	8	Responds appropriately to reasonable changes in routine (for example, refrains from ome_lainin , tc.).	2	1	0	DK	
	9	Says that he or she is sorry for unintended mistakes (for example, bumping into someone, t .).	2	1	0	DK	?
	10	Chooses not to taunt, tease, or bully.	2	1	0	DK	?
	11	Acts appropriately when introduced to strangers (for example, nods, smiles, shakes hands, greets them , etc.).	2	1	0	DK	?
	12	Changes voice level depending on location or situation (for example, in a library, during a movie or play, e	2		0	DK	?
	13	Says he or she is sorry after hurting another's feelings.	2	1	0	DK	?
	14	Refrains from talking with food in mouth.	2	1	0	DK	
	15	Talks with others without interrupting or being rude.	2	1	0	DK	?
	16	Accepts helpful suggestions or solutions from others.	2	1	0	DK	?
	17	Controls anger or hurt feelings when plans change for reason(s) that are not self-inflicted (for example, bad weather, car trouble, etc.).	2	1	0	DK	
	18	Keeps secrets or confidences for longer than one day.	2	1	0	DK	
	19	Says he or she is sorry after making unintentional mistakes or errors in judgment (for example, when unintentionally leaving something out of a game, etc):	2	1	0	DK	?
	1	Shows understanding that gentle teasing with family and friends can be a form of humor or affection.	2	1	0	DK	?
	2	Tells parent or caregiver about his or her plans (for example, what time he or she is leaving and returning, where he or she is going, etc.).	2	1	0	DK	
	3	Chooses to avoid dangerous or risky activities (for example, jumping off high places, picking up a hitchhiker/driving recklessly, etc.).	2	1	0	DK	?
	23	Controls anger or hurt feelings when he or she does not get his or her way (for example, when not allowed to watch television or attend a party; when suggestion is rejected by [redacted]).	2	1	0	DK	?
	24	Follows through with arrangements (for example, if promises to meet someone, meets that person; etc.).	2	1	0	DK	?
	25	Stops or stays away from relationships or situations that are hurtful or dangerous (for example, being bullied or made fun of, being taken advantage of sexually or financially, etc.).	2		0	DK	?
	26	Controls anger or hurt feelings due to constructive criticism (for example, correction of misbehavior, discussion of test score or grade, performance review, etc.).	2	1	0	DK	?
	27	Keeps secrets or confidences for as long as needed.	2	1	0	DK	?
	28	Thinks about what could happen before making decisions (for example, refrains from acting impulsively, thinks about important information, etc.).	2	1	0	DK	?
	29	Is aware of potential danger and uses caution when encountering risky social situations (for example, binge drinking parties, internet chat rooms, personal ads, etc.).	2	1	0	DK	?
	30	Shows respect for co-workers (for example, does not distract or interrupt others who are working, is on time for meetings, etc.).	2		0	DK	?

Physical Activity

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know N/0 = No Opportunity

Using Large Muscles

							Circle "1" If You Have a Question
Start Ages 0-1	1	Holds head erect for at least 15 seconds when held upright in parent's or caregiver's arms.	2		0	D K	?
	2	Sits supported (for example, in a chair, with pillows, etc.) for at least 1 minute.	2		0	DK	?
	3	Sits without support for at least 1 minute.	2		0	DK	?
	4	Creeps or moves on stomach across floor.	2		0	DK	?
	5	Sits without support for at least 10 minutes.			0	K	1
	6	Raises self to sitting position and sits without support for at least 1 minute.	2	1	0	K	?
	7	Crawls at least 5 feet on hands and knees, without stomach touching floor.	2		0	K	?
	8	Pulls self to standing position.	2	1	0	DK	?
	9	Crawls up stairs.	2		0	DK	?
	10	Takes at least two steps.	2	1	0	K	?
	11	Stands alone for 1 to 3 minutes.	2		0	D	?
	12	Rolls ball while sitting.	2		0	DK	?
	13	Climbs on and off low objects (for example, chair, step stool, slide, etc.).	2		0	DK	?
	14	Crawls down stairs.	2		0	DK	1
	15	Stands for at least 5 minutes.	2	1	0	DK	1
Start Ages 2-4	16	Walks across room; may be unsteady and fall occasionally.	2	1	0	DK	?
	17	Throws ball.	2	1	0	DK	?
	18	Walks to get around; does not need to hold on *to* anything.	2	1	0	DK	1
	19	Climbs on and off adult-sized chair.	2	1	0	DK	?
	20	Runs without falling; may be awkward and uncoordinated.	2	1	0	DK	1
	21	Walks up stairs, putting both feet on each step; may use railing.	2	1	0	DK	?
	22	Kicks ball.	2	1	0	DK	?
	23	Runs smoothly without falling.	2	1	0	DK	?
	24	Walks down stairs, facing forward, putting both feet on each step; may use railing.	2	1	0	DK	?
	25	Jumps with both feet off floor.	2	1	0	DK	
Start Ages 4-5	26	Throws ball of any size in specific direction.	2	1	0	DK	?
	27	Catches beach ball-sized ball with both hands from a distance of 2 or 3 feet.	2	1	0	DK	?
	28	Walks up stairs, alternating feet; may use railing.	2	1	0	DK	1
	29	Pedals tricycle or other three-wheeled toy for at least 6 feet.	2		0	OK	
		Scoring Tip: You may mark "N/0" for No Opportunity if the individual does not have a tricycle or three-wheeled toy. However, if the individual has such a vehicle but does not ride it for any reason, including parent or caregiver does not think he or she is ready, mark "0."			N/O		
	30	Jumps or hops forward at least three times.	2		0	DK	1
	31	Hops on one foot at least once without falling; may hold on to something for balance.	2	1	0	DK	?

Physical Activity conti e

Response Options: 2 = Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know N/0 = No Opportunity

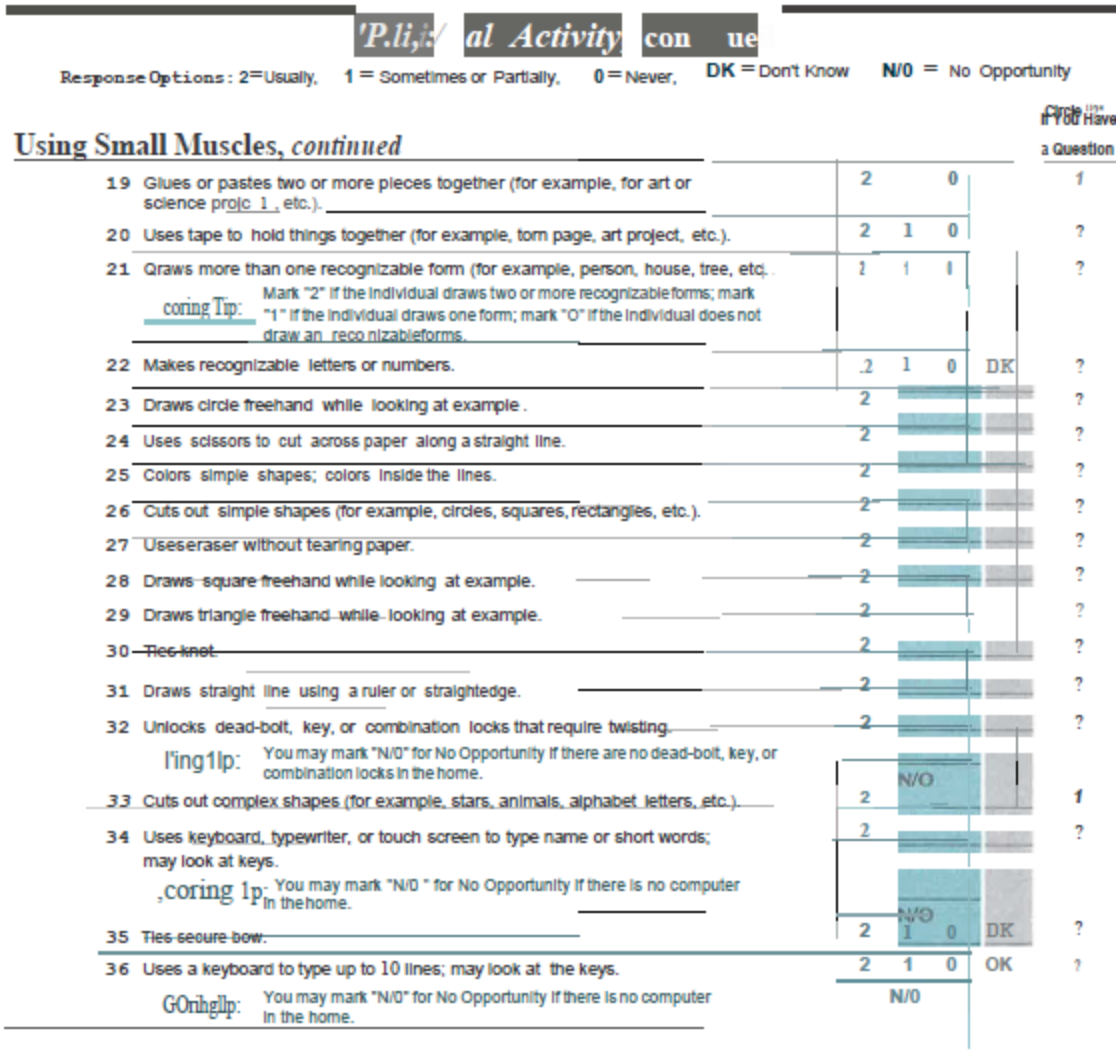
Using Large Muscles, *continued*

						Circle "?" If You Have a Question
	32	Climbs on and off high objects (for example, jungle gym, 4-foot slide ladder, etc.).	2	1	0	DK	?
	33	Walks down stairs, alternating feet; may use railing.	2	1	0	DK	?
	34	Runs smoothly, with changes in speed and direction.	2	1	0	DK	?
	35	Rides bicycle with training wheels for at least 10 feet.				DK	
		Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a bicycle. However, if the individual has a bike but does not ride it for any reason, including parent or caregiver does not think he or she is ready, mark "0."		N/0			
	36	Catches beach ball-sized ball (from at least 6 feet away) with both hands.	2	1	0	DK	?
	37	Hops forward on one foot with ease.	2	1	0	DK	?
	38	Skips at least 5 feet.	2	1	0	DK	?
	39	Catches tennis or baseball-sized ball (from at least 10 feet away), moving to catch it if necessary.	2	1	0	DK	?
	40	Rides bicycle with no training wheels without falling.	2	1	0	DK	?
		Scoring Tip: You may mark "N/O" for No Opportunity if the individual does not have a bicycle. However, if the individual has a bike but does not ride it for any reason, including parent or caregiver does not think he or she is ready, mark "0."		N/0			

Using Small Muscles

						Circle "?" If You Have a Question
Start Ages 0-4	1	Reaches for toy or object.	2	1	0	DK	?
	2	Picks up small objects (no larger than 2 inches on any side); may use both hands.	2	1	0	DK	?
	3	Moves object from one hand to the other.	2	1	0	DK	
	4	Squeezes squeaky toy or object.	2	1	0	DK	?
	5	Picks up small object with thumb and fingers.	2	1	0	DK	
	6	Removes object (for example, a block or clothespin) from a container.	2	1	0	OK	?
	7	Puts object (for example, a block or clothespin) into a container.	2	1	0	DK	?
	8	Turns pages of board, cloth, or paper book, one at a time.	2	1	0	DK	?
	9	Stacks at least four small blocks or other small objects; stack must not fall.	2	1	0	DK	?
	10	Opens doors by turning doorknobs.	2	1	0	DK	?
Start Ages 5-6	11	Unwraps small objects (for example, gum or candy).	2	1	0	DK	?
	12	Completes simple puzzle of at least two pieces or shapes.	2	1	0	DK	?
	13	Turns book or magazine pages one by one.	2	1	0	DK	?
	14	Uses twisting hand-wrist motion (for example, winds up toy, screws/unscrews lid of jar, etc.).	2	1	0	OK	
	15	Holds pencil in proper position (not with fist) for writing or drawing.	2	1	0	DK	?
	16	Colors simple shapes; may color outside lines.	2	1	0	DK	?
	17	Builds three-dimensional structures (for example, a house, bridge, vehicle, etc.) with at least five small blocks.	2	1	0	DK	?
	18	Opens and closes scissors with one hand.	2	1	0	DK	?

19



'P.li,;/ al Activity con ue

Response Options: 2=Usually, 1 = Sometimes or Partially, 0 = Never, DK = Don't Know N/0 = No Opportunity

Using Small Muscles, *continued*

Circle Line If You Have a Question

19	Glues or pastes two or more pieces together (for example, for art or science proje 1 , etc.).	2		0		1
20	Uses tape to hold things together (for example, torn page, art project, etc.).	2	1	0		?
21	Draws more than one recognizable form (for example, person, house, tree, etc.	2	1	0		?
	coring Tip: Mark "2" if the individual draws two or more recognizable forms; mark "1" if the individual draws one form; mark "O" if the individual does not draw an reco nizableforms.					
22	Makes recognizable letters or numbers.	2	1	0	DK	?
23	Draws circle freehand while looking at example .	2				?
24	Uses scissors to cut across paper along a straight line.	2				?
25	Colors simple shapes; colors inside the lines.	2				?
26	Cuts out simple shapes (for example, circles, squares, rectangles, etc.).	2				?
27	Useseraser without tearing paper.	2				?
28	Draws square freehand while looking at example.	2				?
29	Draws triangle freehand while looking at example.	2				?
30	Ties knot.	2				?
31	Draws straight line using a ruler or straightedge.	2				?
32	Unlocks dead-bolt, key, or combination locks that require twisting.	2				?
	l'ing1lp: You may mark "N/0" for No Opportunity if there are no dead-bolt, key, or combination locks in the home.			N/O		
33	Cuts out complex shapes (for example, stars, animals, alphabet letters, etc.).	2				1
34	Uses keyboard, typewriter, or touch screen to type name or short words; may look at keys.	2				?
	,coring 1p: You may mark "N/0 " for No Opportunity if there is no computer in the home.			N/O		
35	Ties secure bow.	2	1	0	DK	?
36	Uses a keyboard to type up to 10 lines; may look at the keys.	2	1	0	OK	?
	GOrihgllp: You may mark "N/0" for No Opportunity if there is no computer in the home.			N/0		

Problem Behaviors Part 1

Response Options: 2 = Often, 1 = Sometimes, 0 = Never

Section A

					Circle "?" If You Have a Question
Start Ages 3+	1	Is overly dependent (that is, clings to caregiver, teacher, brother, or sister).	0	2	
	2	Avoids others and prefers to be alone.	0	2	?
	3	Has eating difficulties (for example, eats too fast or too slowly, hoards food, overeats, refuses to eat, etc.).	0 1	2	?
	4	Has sleep difficulties (for example, sleepwalks, has frequent nightmares, sleeps significantly more or less than typical for his or her age).	0 1	2	
	5	Refuses to go to school or work because of fear, feelings of rejection or isolation, etc.	0		?
	6	Is overly anxious or nervous.	0 1	2	
	7	Cries or laughs too easily.	0	2	
	8	Has poor eye contact (that is, does not look at or face others when speaking or poking to).	0	2	
	9	Is sad for no clear reason.	0	2	?
	10	Avoids social interaction.	0 1	2	
	11	Lacks energy or interest in life.	0 1	2	

Section B

					Circle "?" If You Have a Question
Start Ages 3+	1	Is impulsive (that is, acts without thinking).	0 1	2	?
	2	Has temper tantrums.	0 1	2	?
	3	Intentionally disobeys and defies those in authority.	0 1	2	
	4	Taunts, teases, or bullies.	0 1	2	?
	5	Is inconsiderate or insensitive to others.	0 1	2	
	6	Lies, cheats, or steals.	0 1	2	
	7	Is physically aggressive (for example, hits, kicks, bites, etc.).	0 1	2	
	8	Is stubborn or sullen.	0 1	2	
	9	Says embarrassing things or asks embarrassing questions in public (for example, "You're fat," or "What's that big reel thing on your nose?").	0 1	2	
	10	Behaves inappropriately at the urging of others.	0 1	2	?

Section C

					Circle "?" If You Have a Question
Start Ages 3+	1	Sucks thumb or fingers.	0 1	2	?
	2	Wets bed or must wear diapers at night.	0 1	2	
	3	Acts overly familiar with strangers (for example, holds hands, hugs, sits on lap, etc.).	0 1	2	
	4	Bites fingernails.	0 1	2	
	5	Has tics (that is, involuntary blinking, twitching, head shaking, etc.).	0 -1	2	?

Problem Behaviors Part 1, continued

Response Options: 2 = Often, 1 = Sometimes, 0 = Never

Section C, *continued*				Circle "?" If You Have a Question
6	Grinds teeth during the day or night.	0	2	?
7	Has a hard time paying attention.	0	2	?
8	Is more active or restless than others of same age.	0	1 2	?
9	Uses school or work property (for example, telephone, internet access, office supplies, etc.) for unapproved personal purposes.	0	1 2	?
10	Swears.	0	2	?
11	Runs away (that is, is missing for 24 hours or longer).	0	2	?
12	Is truant from school or work.	0	1 2	?
13	Ignores or doesn't pay attention to others around him or her.	0	1 2	?
14	Uses money or gifts to "buy" affection.	0		?
15	Uses alcohol or illegal drugs during the school or work day.	0	2	?

Problem Behaviors Part 2

Response Options: 2 = Often, 1 = Sometimes, 0 = Never, S = Severe, M = Moderate

Section D					Circle "?" If You Have a Question
Start Ages 3+	Engages in inappropriate sexual behavior (for example, exposes self, masturbates in public, makes improper sexual advances, etc.).	0	1 2	S	?
2	Is obsessed with objects or activities (for example, constantly repeats words or phrases, is preoccupied with mechanical objects, etc.).	0	1 2	S	?
3	Expresses thoughts that do not make sense (for example, talks about hearing voices, seems delusional, etc.).	0	1 2	S M	?
4	Has strange habits or ways (for example, makes repetitive noises, odd hand movements, etc.).	0	1 2	S M	?
5	Consistently prefers objects to people (for example, pays more attention to objects than to people, etc.).	0	1 2	S M	
6	Displays behaviors that cause injury to self (for example, bangs head, hits or bites self, tears at skin, etc.).	0	1 2	S M	?
7	Destroys own or another's possessions on purpose.	0	1 2	S M	?
8	Uses bizarre speech (for example, has conversations with self in public, speaks in phrases or sentences that have no meaning, repeats same word or phrase over and over, etc.).	0	1 2	S M	?
9	Is unaware of what is happening around him or her (for example, seems to be in a "fr," stares blankly, etc.).	0	1 2	S M	?
10	Rocks back and forth repeatedly.	0	1 2	S M	?
11	Is unusually fearful of ordinary sounds, objects, or situations.	0	1 2	S M	?
12	Remembers odd information in detail years later.	0	1 2	S M	?
13	Is unable to complete a normal school or work day because of chronic pain or fatigue.	0	1 2	S M	?
14	Is unable to complete a normal school or work day because of psychological symptoms.	0	1 2	S M	?

APPENDIX 5 – TANNER STAGING

The Tanner Stages

Because the onset and progression of puberty are so variable, Tanner has proposed a scale, now uniformly accepted, to describe the onset and progression of pubertal changes (Fig. 9-24). Boys and girls are rated on a 5 point scale. Boys are rated for genital development and pubic hair growth, and girls are rated for breast development and pubic hair growth.

Pubic hair growth in females is staged as follows (Fig 9-24, B):

- **Stage I (Preadolescent)** - Vellos hair develops over the pubes in a manner not greater than that over the anterior wall. There is no sexual hair.
- **Stage II** - Sparse, long, pigmented, downy hair, which is straight or only slightly curled, appears. These hairs are seen mainly along the labia. This stage is difficult to quantitate on black and white photographs, particularly when pictures are of fair-haired subjects.
- **Stage III** - Considerably darker, coarser, and curlier sexual hair appears. The hair has now spread sparsely over the junction of the pubes.
- **Stage IV** - The hair distribution is adult in type but decreased in total quantity. There is no spread to the medial surface of the thighs.
- **Stage V** - Hair is adult in quantity and type and appears to have an inverse triangle of the classically feminine type. There is spread to the medial surface of the thighs but not above the base of the inverse triangle.

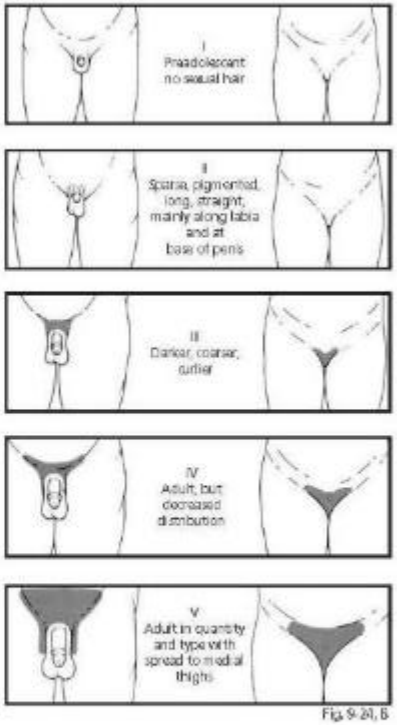


Fig. 9-24, B

The stages in male pubic hair development are as follows (Fig. 9-24, B):

- **Stage I (Preadolescent)** - Vellos hair appears over the pubes with a degree of development similar to that over the abdominal wall. There is no androgen-sensitive pubic hair.
- **Stage II** - There is sparse development of long pigmented downy hair, which is only slightly curled or straight. The hair is seen chiefly at the base of penis. This stage may be difficult to evaluate on a photograph, especially if the subject has fair hair.
- **Stage III** - The pubic hair is considerably darker, coarser, and curlier. The distribution is now spread over the junction of the pubes, and at this point that hair may be recognized easily on black and white photographs.
- **Stage IV** - The hair distribution is now adult in type but still is considerably less that seen in adults. There is no spread to the medial surface of the thighs.
- **Stage V** - Hair distribution is adult in quantity and type and is described in the inverse triangle. There can be spread to the medial surface of the thighs.

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In young women, the Tanner stages for breast development are as follows (Fig. 9-24, C):

- **Stage I (Preadolescent)** - Only the papilla is elevated above the level of the chest wall.
- **Stage II - (Breast Budding)** - Elevation of the breasts and papillae may occur as small mounds along with some increased diameter of the areolae.
- **Stage III** - The breasts and areolae continue to enlarge, although they show no separation of contour.
- **Stage IV** - The areolae and papillae elevate above the level of the breasts and form secondary mounds with further development of the overall breast tissue.
- **Stage V** - Mature female breasts have developed. The papillae may extend slightly above the contour of the breasts as the result of the recession of the aerolae.

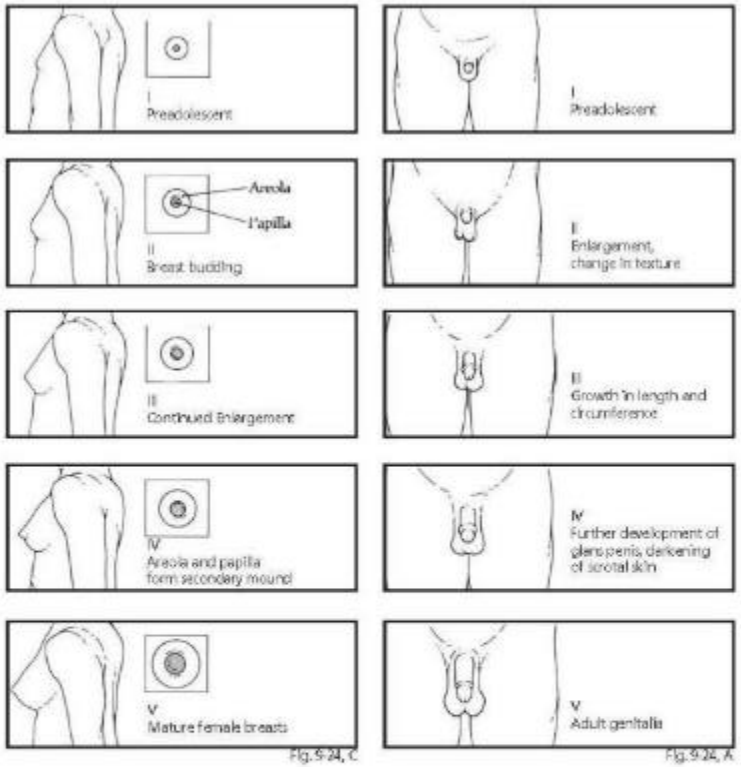

Fig. 9-24, C Fig. 9-24, A

The stages for male genitalia development are as follows: (Fig. 9-24, A):

- **Stage I (Preadolescent)**- The testes, scrotal sac, and penis have a size and proportion similar to those seen in early childhood.
- **Stage II** - There is enlargement of the scrotum and testes and a change in the texture of the scrotal skin. The scrotal skin may also be reddened, a finding not obvious when viewed on a black and white photograph.
- **Stage III** - Further growth of the penis has occurred, initially in length, although with some increase in circumference. There also is increased growth of the testes and scrotum.
- **Stage IV** - The penis is significantly enlarged in length and circumference, with further development of the glans penis. The testes and scrotum continue to enlarge, and there is distinct darkening of the scrotal skin. This is difficult to evaluate on a black-and-white photograph.
- **Stage V** - The genitalia are adult with regard to size and shape.

Source:

Reprinted with permission from Feingold, David. "Pediatric Endocrinology" in *Atlas of Pediatric Physical Diagnosis, Second Edition*, Philadelphia. W.B. Saunders, 1992, 9.16-19

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APPENDIX 6 – QOLCE QUALITY OF LIFE

QUALITY OF LIFE IN CHILDHOOD EPILEPSY QUESTIONNAIRE

Parent Form

INSTRUCTIONS

1. This questionnaire asks about your child's day to day functioning in various life areas. It looks at how you see epilepsy affecting your child's day to day functioning. Your answers will be confidential.

2. If you choose not to participate it will not affect the care you or your child receive.

3. Please answer the questions by marking the appropriate box, like this... ☑

4. Certain questions may look alike, but each one is different. Some questions ask about problems your child may not have, but it's important for us to know this information too. Please answer each question to the best of your knowledge. Remember to answer all questions unless instructed otherwise.

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

6. All comments will be read, so please feel free to make as many as you wish.

7. You may not be able to answer some questions about your child. For example, it may be difficult to tell how your child feels because s/he is too young or where disability prevents your child talking about their feelings. In such cases the "Not Applicable" response is appropriate.

SECTION 3: YOUR CHILD'S PHYSICAL ACTIVITIES

The following questions ask about physical activities your child might do.

3.1. In his/her daily activities during the past 4 weeks, how often has your child:

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
a. needed more supervision than other children his/her age?	☐	☐	☐	☐	☐	☐
b. needed special precautions (ie wearing a helmet)?	☐	☐	☐	☐	☐	☐
c. played freely in the house like other children his/her age?	☐	☐	☐	☐	☐	☐
d. played freely outside the house like other children his/her age?	☐	☐	☐	☐	☐	☐
e. gone swimming? (ie. swam independently)	☐	☐	☐	☐	☐	☐
f. participated in sports activities (other than swimming)?	☐	☐	☐	☐	☐	☐
g. stayed out overnight (with friends or family)?	☐	☐	☐	☐	☐	☐
h. played with friends away from you or your home	☐	☐	☐	☐	☐	☐
i. gone to parties without you or without supervision?	☐	☐	☐	☐	☐	☐
j. been able to do the physical activities other children his/her age do?	☐	☐	☐	☐	☐	☐

3

3.2. During the past 4 weeks how much of the time do you think your child:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	Not Applicable
a. felt tired	☐	☐	☐	☐	☐	☐
b. felt energetic	☐	☐	☐	☐	☐	☐

3.3 Is there anything else you would like to tell us about your child's activities?

SECTION 4: WELL-BEING

Below is a list that describes how your child might feel in general.

4.1. During the past 4 weeks, how much of the time do you think your child

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	Not applicable
a. felt down or depressed?	☐	☐	☐	☐	☐	☐
b. felt calm?	☐	☐	☐	☐	☐	☐
c. felt helpless in situations?	☐	☐	☐	☐	☐	☐
d. felt happy?	☐	☐	☐	☐	☐	☐
e. wished s/he was dead?	☐	☐	☐	☐	☐	☐
f. felt in control?	☐	☐	☐	☐	☐	☐
g. felt tense and anxious?	☐	☐	☐	☐	☐	☐
h. felt frustrated?	☐	☐	☐	☐	☐	☐
i. felt overwhelmed by events?	☐	☐	☐	☐	☐	☐
j. worried a lot?	☐	☐	☐	☐	☐	☐
k. felt confident?	☐	☐	☐	☐	☐	☐
l. felt excited or interested in something?	☐	☐	☐	☐	☐	☐
m. felt pleased about achieving something?	☐	☐	☐	☐	☐	☐
n. got easily embarrassed?	☐	☐	☐	☐	☐	☐
o. felt different or singled out?	☐	☐	☐	☐	☐	☐
p. felt nobody understood him/her?	☐	☐	☐	☐	☐	☐
q. felt valued?	☐	☐	☐	☐	☐	☐
r. felt s/he was not good at anything?	☐	☐	☐	☐	☐	☐
s. felt no one cared?	☐	☐	☐	☐	☐	☐

5

4.2. Is there anything else you would like to tell us about how your child feels in general?

6

SECTION 5: COGNITION

The following questions ask about some problems children have with concentrating, remembering, and speaking.

5.1. Compared to other children of his/her own age, how often during the past 4 weeks has your child

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
a. had difficulty attending to an activity ?	☐	☐	☐	☐	☐	☐
b. had difficulty reasoning or solving problems?	☐	☐	☐	☐	☐	☐
c. had difficulty making plans or decisions?	☐	☐	☐	☐	☐	☐
d. had difficulty keeping track of conversations?	☐	☐	☐	☐	☐	☐
e. had trouble concentrating on a task?	☐	☐	☐	☐	☐	☐
f. had difficulty concentrating on reading?	☐	☐	☐	☐	☐	☐
g. had difficulty doing one thing at a time?	☐	☐	☐	☐	☐	☐
h. reacted slowly to things being said & done?	☐	☐	☐	☐	☐	☐
i. completed activities that needed organising & planning?	☐	☐	☐	☐	☐	☐
j. found it hard remembering things?	☐	☐	☐	☐	☐	☐
k. had trouble remembering names of people?	☐	☐	☐	☐	☐	☐
l. had trouble remembering where s/he put things?	☐	☐	☐	☐	☐	☐
m. had trouble remembering things people told him/her?	☐	☐	☐	☐	☐	☐

5.1. continued: Compared to other children his/her own age, how often during the past 4 weeks has your child

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
n. had trouble remembering things s/he read hours or days before?	☐	☐	☐	☐	☐	☐
o. planned to do something then forgot?	☐	☐	☐	☐	☐	☐
p. had trouble finding the correct words?	☐	☐	☐	☐	☐	☐
q. had trouble understanding or following what others were saying?	☐	☐	☐	☐	☐	☐
r. had trouble understanding directions?	☐	☐	☐	☐	☐	☐
s. had difficulty following simple instructions?	☐	☐	☐	☐	☐	☐
t. had difficulty following complex instructions?	☐	☐	☐	☐	☐	☐
u. had trouble understanding what s/he read?	☐	☐	☐	☐	☐	☐
v. had trouble writing?	☐	☐	☐	☐	☐	☐
w. had trouble talking	☐	☐	☐	☐	☐	☐

5.2. Is there anything else you would like to tell us about your child's concentration, memory or speech?

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SECTION 6: YOUR CHILD'S SOCIAL ACTIVITIES

6.1. During the past 4 weeks, how often has your child's epilepsy

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
a. limited his/her social activities (visiting friends, close relatives, or neighbours?	☐	☐	☐	☐	☐	☐
b. helped him/her to make friends?	☐	☐	☐	☐	☐	☐
c. affected his/her social interactions at school or work?	☐	☐	☐	☐	☐	☐
d. improved his/her friendships & relationships with others?	☐	☐	☐	☐	☐	☐
e. limited his/her leisure activities (hobbies or interests)?	☐	☐	☐	☐	☐	☐
f. isolated him/her from others?	☐	☐	☐	☐	☐	☐
g. improved his/her relations with family members?	☐	☐	☐	☐	☐	☐
h. made it difficult for him/her to keep friends?	☐	☐	☐	☐	☐	☐
i. frightened other people	☐	☐	☐	☐	☐	☐

6.2. During the past 4 weeks, how limited are your child's social activities compared with others his/her age because of his/her epilepsy or epilepsy-related problems?

☐ Yes, limited a lot	☐ Yes, limited some	☐ Yes, limited a little	☐ Yes, but rarely	☐ No, not limited

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6.3. During the past 4 weeks, how often has your child freely discussed his/her epilepsy with friends?

☐ Very often ☐ Fairly often ☐ Sometimes ☐ Almost never ☐ Not applicable

6.4. During the past 4 weeks, how often has your child freely discussed his/her epilepsy with family?

☐ Very often ☐ Fairly often ☐ Sometimes ☐ Almost never ☐ Not applicable

6.5. Is there anything else you would like to tell us about your child's social activities?

SECTION 7: YOUR CHILD'S BEHAVIOUR

Below are statements that describe some children's behaviour.
Please answer all questions as well as you can, even if some do not seem to apply to your child.

7.1. Compared to other children his/her own age, how often during the past 4 weeks do each of the following statements describe your child?

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
a. relied on you / family to do things for him/her that s/he was able to do him/herself	☐	☐	☐	☐	☐	☐
b. asked for reassurance	☐	☐	☐	☐	☐	☐
c. was socially inappropriate (said or did something out of place in a social situation)	☐	☐	☐	☐	☐	☐
d. wanted things to be perfect	☐	☐	☐	☐	☐	☐
e. did not give up easily	☐	☐	☐	☐	☐	☐
f. angered easily	☐	☐	☐	☐	☐	☐
g. hit or attacked people	☐	☐	☐	☐	☐	☐
h. swore in public	☐	☐	☐	☐	☐	☐
i. joined in activities with other children	☐	☐	☐	☐	☐	☐
j. feared unfamiliar places, situations or people	☐	☐	☐	☐	☐	☐
k. preferred his/her own company instead of seeking out others	☐	☐	☐	☐	☐	☐
l. was obedient	☐	☐	☐	☐	☐	☐
m. set high standards for self	☐	☐	☐	☐	☐	☐
n. did not worry about what others thought	☐	☐	☐	☐	☐	☐
o. got along with other children	☐	☐	☐	☐	☐	☐
p. wished s/he was someone or somewhere else	☐	☐	☐	☐	☐	☐

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7.1 continued: Compared to other children his/her own age, how often during the past 4 weeks do each of the following statements describe your child?

	Very Often	Fairly Often	Sometimes	Almost Never	Never	Not Applicable
q. acted without thinking	☐	☐	☐	☐	☐	☐
r. demanded a lot of attention	☐	☐	☐	☐	☐	☐
s. was decisive	☐	☐	☐	☐	☐	☐
t. was independent	☐	☐	☐	☐	☐	☐
u. preferred routines or disliked changes	☐	☐	☐	☐	☐	☐
v. did things just to prove s/he could	☐	☐	☐	☐	☐	☐
w. preferred the company of adults	☐	☐	☐	☐	☐	☐

7.2. Is there anything else you would like to tell us about your child's behaviour?

SECTION 8: GENERAL HEALTH

8.1. Compared to other children his/her age , how good do you think your child's health has been in the past 4 weeks? Please consider your child's epilepsy as part of his/her health when you answer this question.

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

8.2. Is there anything else you would like to tell us about how epilepsy has affected your child's health?

SECTION 9: QUALITY OF LIFE

9.1. In the past 4 weeks what has your child's quality of life been?

☐ Excellent ☐ Very Good ☐ Good ☐ Fair ☐ Poor

10.0 This questionnaire was completed by the child's

☐ mother
☐ father
☐ both parents
☐ other carers

If you would like a copy of any publications arising from this study, please complete the detachable sheet following. Thank you for your participation.

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Request for copy of any publications arising from this study

Your Name .....

Your Child's Name .....

Your Address .....

.....

.....

APPENDIX 7 – HOSPITAL ANXIETY AND DEPRESSION SCALE

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D)
0-7 = Normal
8-10 = Borderline abnormal (borderline case) 11-21 = Abnormal(case)

APPENDIX 8 – ZARIT CAREGIVER BURDEN INVENTORY

The Zarit Burden Interview

0: NEVER
1: RARELY
2: SOMETIMES
3: QUITE FREQUENTLY
4: NEARLY ALWAYS

Please circle the response the best describes how you feel.

Question	Score
1 Do you feel that your relative asks for more help than he/she needs?	0 1 2 3 4
2 Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	0 1 2 3 4
3 Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	0 1 2 3 4
4 Do you feel embarrassed over your relative's behaviour?	0 1 2 3 4
5 Do you feel angry when you are around your relative?	0 1 2 3 4
6 Do you feel that your relative currently affects our relationships with other family members or friends in a negative way?	0 1 2 3 4
7 Are you afraid what the future holds for your relative?	0 1 2 3 4
8 Do you feel your relative is dependent on you?	0 1 2 3 4
9 Do you feel strained when you are around your relative?	0 1 2 3 4
10 Do you feel your health has suffered because of your involvement with your relative?	0 1 2 3 4
11 Do you feel that you don't have as much privacy as you would like because of your relative?	0 1 2 3 4
12 Do you feel that your social life has suffered because you are caring for your relative?	0 1 2 3 4

Question	Score
13 Do you feel uncomfortable about having friends over because of your relative?	0 1 2 3 4
14 Do you feel that your relative seems to expect you to take care of him/her as if you were the only one he/she could depend on?	0 1 2 3 4
15 Do you feel that you don't have enough money to take care of your relative in addition to the rest of your expenses?	0 1 2 3 4
16 Do you feel that you will be unable to take care of your relative much longer?	0 1 2 3 4
17 Do you feel you have lost control of your life since your relative's illness?	0 1 2 3 4
18 Do you wish you could leave the care of your relative to someone else?	0 1 2 3 4
19 Do you feel uncertain about what to do about your relative?	0 1 2 3 4
20 Do you feel you should be doing more for your relative?	0 1 2 3 4
21 Do you feel you could do a better job in caring for your relative?	0 1 2 3 4
22 Overall, how burdened do you feel in caring for your relative?	0 1 2 3 4

Interpretation of Score:

0 - 21 little or no burden
21 - 40 mild to moderate burden
41 - 60 moderate to severe burden
61 - 88 severe burden

APPENDIX 9 – MAXIMUM ALLOWABLE BLOOD DRAW VOLUMES

Seattle Children's
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Maximum allowable blood draw volumes:

PATIENT'S WEIGHT		TOTAL VOLUME	MAXIMUM mL IN ONE BLOOD DRAW	MAXIMUM mL IN A 30-DAY PERIOD
Kg	lbs	mL	2.5% of total blood vol	5% of total blood vol
1	2.2	100	2.5	5
2	4.4	200	5	10
3	3.3	240	6	12
4	8.8	320	8	16
5	11	400	10	20
6	13.2	480	12	24
7	15.4	560	14	28
8	17.6	640	16	32
9	19.8	720	18	36
10	22	800	20	40
11 thru 15	24 thru 33	880-1200	22-30	44-60
16 thru 20	35 thru 44	1280-1600	32-40	64-80
21 thru 25	46 thru 55	1680-2000	42-50	64-100
26 thru 30	57 thru 66	2080-2400	52-60	104-120
31 thru 35	68 thru 77	2480-2800	62-70	124-140
36 thru 40	79 thru 88	2880-3200	72-80	144-160
41 thru 45	90 thru 99	3280-3600	82-90	164-180
46 thru 50	101 thru 110	3680-4000	92-100	184-200
51 thru 55	112 thru 121	4080-4400	102-110	204-220
56 thru 60	123 thru 132	4480-4800	112-120	224-240
61 thru 65	134 thru 143	4880-5200	122-130	244-260
66 thru 70	145 thru 154	5280-5600	132-140	264-280
71 thru 75	156 thru 165	5680-6000	142-150	284-300
76 thru 80	167 thru 176	6080-6400	152-160	304-360
81 thru 85	178 thru 187	6480-6800	162-170	324-340
86 thru 90	189 thru 198	6880-7200	172-180	344-360
91 thru 95	200 thru 209	7280-7600	182-190	364-380
96 thru 100	211 thru 220	7680-8000	192-200	384-400

Based on blood volume of:
1 to 2 kg 100 mL/kg (pre-term infant)
>2 kg 80 mL/kg (term infant - adult)
This information is similar to that used by the Committee on Clinical Investigations at Children's Hospital in Los Angeles, and at Baylor College of Medicine in Dallas, TX.

Adapted by Rhona Jack, Ph.D. August 2001
Children's Hospital and Regional Medical Center Laboratory
Seattle, WA

APPENDIX 10 – STUDY CONDUCT DURING COVID-19

In March 2020, the World Health Organization declared a global pandemic related to an illness caused by a novel coronavirus known as COVID-19. As a result, public health initiatives, such as laws, regulations and policies were enacted at country and institutional levels to protect the health of the general public. These initiatives and policies have affected the ability of study sites to conduct the trial per protocol and the ability of the sponsor and/or delegate to conduct trial oversight and monitoring visits.

In an effort to support the rights, safety and welfare of subjects and ensure as little impact on the integrity of the research as possible the following alternative processes have been implemented due to restrictions related to COVID-19. Though every attempt should be made to conduct study visits per protocol, any implementation of alternative processes should be properly documented.

1. Allowance of Delays to In-person Study Visits

If sites are unable to conduct study visits, or subjects are unable to travel to the study site due to COVID-19 circumstances, an in-person visit may be delayed up to 6 weeks from the protocol-defined visit due date. Data will need to be entered per normal procedures in the EDC, with a description indicating COVID-19 as the cause for delay in response to queries. If a subject is unable to travel to the study site within this expanded 6-week window, a telephone or video telemedicine visit should be attempted, as described below. If a telephone or video telemedicine visit cannot be conducted in the 6-week window, the visit should be considered missed and the next scheduled visit conducted.

2. Allowance of Remote Telemedicine/Telephone/Video Visits:

Visits 1-5 should be conducted in person. For Visits 6, 8, 10, 15-21, remote visits via telephone or video are acceptable when subjects are unable to travel to the site for in-person visits due to COVID-19 circumstances. The following information should be collected and recorded in the source documentation and in the EDC where applicable. Log pages (e.g. AEs, concomitant medication changes) will be entered normally as they are not associated with specific visits; assessment forms located within a particular visit page will also be entered normally, however, queries will be fired to capture specific information explaining the basis for missing or alternatively collected (ie. remote) data. Detailed instruction for EDC entry may be found in the CRF Completion Guidelines (CCGs).

- Date and time of the telephone/video visit
- Any changes in health status
- AEs/SAE assessment
- Concomitant medication query
- Review seizure and medication diary with parent/caregiver for compliance and any abnormalities in seizure activity
- Scales and Questionnaires, when applicable and if feasible
  - C-SSRS
  - CGI-I (by Investigator and Parent/Caregiver)
  - BRIEF
  - Tanner Staging
  - QOLCE
  - Zarit Caregiver Burden
  - HADS

3. End-of-Study/Early Termination (EOS/ET) and Follow-up Visits:

Cardiac follow-up visits (Visits 14, 24, or 25) must be conducted in-person.

EOS/ET for subjects tapering off ZX008:
For the EOS/ET visit (Visit 12 or 22) and Post-Dosing Follow-up visit (Visit 13 or 23), every attempt should be made to conduct these visits in-person. For subjects tapering off study-drug that are unable to come to the study site, the EOS/ET and Post-Dosing Follow-up visits may be conducted via telephone or video. However, subjects should return to the study site in person, as soon as feasible to conduct any safety assessments that were unable to be evaluated remotely. If an in-person visit cannot be scheduled within 6 months of the EOS/ET and/or Post-Dosing Follow-up visit windows to conduct the required safety assessments, these assessments will be considered as missed.

EOS/ET for subjects transitioning to another Extension Study:
For subjects transitioning into another ZX008 extension study that are unable to attend the EOS/ET visit due to restrictions to traveling to the study site, delays in the start-up of the extension study, or other COVID-related delays, the EOS/ET visit may be delayed until an in-person visit is conducted. Therefore, subjects may remain on study for longer than the planned duration of participation. If the delay is over 6 weeks, medical monitor review and approval is required. If approval to extend beyond 6 weeks is granted, telephone or video visits should be conducted at least every 12 weeks until the in-person EOS/ET transitional visit to the other extension study is performed. The telephone or video visits will collect the following data, at minimum:

- Date and time of the telephone/video visit
- Any changes in health status
- AEs/SAE assessment
- Concomitant medication query
- Review seizure and medication diary with parent/caregiver for compliance and any abnormalities in seizure activity

4. Allowance of delays to ECHO, ECG, Chest X-Ray, EEG and clinical lab assessments when in-person study visits are missed or delayed

If it is not possible to obtain the above assessments as described below, a documented risk/benefit discussion with the medical monitor is required to determine a course of action, which may include approval to delay further for a pre-specified duration, subject withdrawal, or other actions. The risk/benefit analysis will take into account AEs, previous assessment findings, duration of delay, clinical improvement while on study drug (seizure and non-seizure outcomes), and region-specific risk of attending in-person visits to complete the assessments.

Doppler ECHO:

If subjects are unable to travel to the study site due to COVID-19 circumstances, ECHOs may be delayed up to an additional 3 months from the protocol-designated ECHO due date (for a total of 6 months from the time of the last ECHO) for subjects that exhibited the following on their previous, most recent ECHO: absent aortic regurgitation, absent or trace mitral regurgitation, and PASP <30 mmHg.

All subjects with regurgitation ≥ trace aortic regurgitation, ≥mild mitral regurgitation, or PASP ≥30 mmHg may have ECHO delayed from the protocol-designated ECHO due date by up to 6 weeks

only.

In those cases where an ECHO cannot be performed in the specified time period at the study-authorized facility by a certified sonographer, the Sponsor may approve administration of the ECHO at an alternative facility to minimize need for travel. If needed, the sponsor will provide a list of pediatric ECHO centers ('brick and mortar' locations) certified by the Intersocietal Accreditation Commission (IAC). If the ECHO cannot be performed, a benefit risk/benefit analysis must be conducted as described above.

If a delayed ECHO was conducted within 30 days of a scheduled Cardiac Follow-up Visit and there were no findings meeting Level 2 criteria (see Protocol Table 17), the Cardiac Follow-up Visit may be cancelled. If Level 2 or greater findings were observed, then the Cardiac Follow-up Visit should be rescheduled 3 months from the date of the delayed ECHO.

ECG, Chest X-ray and EEG:

If clinically indicated and where applicable, delays in these assessments may be implemented based on the investigators' clinical discretion, weighing the risk/benefit of the clinical necessity of the assessment versus the risk of an in-person visit. All decisions should be documented appropriately in the source documentation. If not conducted at the study site, ECG, chest X-ray and EEG can be performed at any qualified local facility with results sent to the Principal Investigator for safety overread and documentation.

If the ECG (or in the case of certain country-specific regulations: Chest X-ray or EEG) was conducted within 30 days of a scheduled Cardiac Follow-up Visit, these assessments do not need to be repeated at the Cardiac Follow-up Visit provided there were no significant findings that require additional follow-up.

Clinical Laboratory Assessments:

If clinically indicated and where applicable, delays in these assessments may be implemented based on the investigators' clinical discretion, weighing the risk/benefit of the clinical necessity of the assessment versus the risk of an in-person visit. All decisions should be documented appropriately in the source documentation. If not conducted at the study site, clinical laboratory assessments can be performed at any qualified local facility with results sent to the Principal Investigator for safety overread and documentation.

5. Alternative Dispensation for Study Drug

Shipments of investigational product may be sent by courier from site pharmacy to the subject's home via Sponsor-approved processes if the subject cannot or will not attend the dispensation visit(s). This shipment of drug should be arranged for patients who are due in the clinic for a drug dispensation visit. Other alternative dispensation, such as curbside pickup, may be implemented provided they are approved by the Sponsor and appropriate safeguards are taken to ensure compliance with existing regulatory requirements for maintaining investigational product accountability. Detailed instructions for drug handling, storage, accountability, etc. are described in the Pharmacy Manual.

APPENDIX 11 - SUMMARY OF PROTOCOL AMENDMENT 3.0

Amendment 3.0 includes study conduct information for the COVID-19 pandemic. This amendment also removes the Vineland Adaptive Behavior Scale (VABS) from the study assessments, includes updated IP storage excursions to align with updates to the Pharmacy Manual, and provides updated Background information related to existing treatments for LGS and additional clinical and pre-clinical study data.

List of Specific Changes
Additions are marked in **red** and deletions are marked in ~~strikethrough~~. Minor editorial and nonsubstantive changes, such as the correction of typing or formatting errors, updated use of abbreviations, updating headers and footers, tables of contents, list of abbreviations, signature pages, etc., are not listed. The list of specific changes below is grouped by rationale and not necessarily presented in the order in which they appear in the protocol.

1. Removal of VABS as a study assessment in Part 2; due to an error in the version programmed for electronic administration, the subject/caregiver was presented with fewer questions than required to determine standard scores. As we are unable to make meaningful determinations from the instrument, the data no longer need to be collected from subjects currently in the trial.

Synopsis/Exploratory Objectives Part 2 and Section 2.2.3

The exploratory objectives of Part 2 are:

- To determine the incidence of the following on subjects receiving ZX008:
  - The incidence of medical services used to treat seizures
  - The incidence of status epilepticus
  - The use of rescue medication
- To assess the effect of ZX008 on the following measures:
  - ~~The change from baseline in behavior using the~~ VABS
  - The change from baseline in 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)

Synopsis/Exploratory Endpoints and Section 2.3.3

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

- The incidence of medical services used to treat seizures
- The incidence of status epilepticus
- Incidence of rescue medication usage
- Number of days rescue medication used
- The change from baseline in behavior using the Vineland Adaptive Behavior Scale (VABS) (Part 1 only)
- The change from baseline in quality of life using the QOLCE
- The change from baseline in caregiver burden using the Zarit Caregiver Burden Inventory
- The change from baseline in affective symptoms of parent/caregiver using the HADS scale

Schedule of Assessments/footnotes Part 2

Table 2. Schedule of Assessments: Part 2

Study Assessments – PART 2	OLE Treatment Period**					Post-Dosing	Cardiac Follow-up
Visit Number	**Visit 15[a]**	**Visit 16[b]**		**Visits 17-21 (Months 1, 2, 3, 6 and 9**)**	**Visit 22[c] (EOS/ET) Month 12**	**Visit 23**	**Visit 24 and 25**
OLE Study Day	**1[a]**	**15**		**30, 60, 90, 180, and 270**	**365**	**379[k,q]**	**(3-24 months post last dose)[d, k]**
		Clinic	**Phone**				
Informed Consent	X						
Entry Criteria	X						
Demographics	X[a]						
Medical/Neurological History	X[a]						
Epilepsy History	X[a]						
Physical Examination, complete	X[a]				X		X
Physical Examination, abbreviated		X[m]		X[m]		X[m]	X
Neurological Examination, complete	X[e]				X		
Neurological Examination, abbreviated		X[m]		X[m]		X[m]	
Vital signs	X	X		X	X		
Weight	X[a]	X		X	X	X	
Height	X[a]				X		
12-lead ECG	X[a]			X	X		X
Doppler ECHO	X[a]			X[f,g]	X		X
EEG (Italy only)	X			X[p]	X		
Chest x-ray (France, Netherlands only)					X		X
Urine or Serum Pregnancy Test[h]	X[a]			X[n]	X		
Clinical laboratory evaluation (hematology/chemistry/urinalysis[c], etc.)	X[i]	X[i]		X[n]	X		
Whole blood CBD/ THC Panel	X[a]			X[n]	X		
Plasma sample for background AEDs		X[m]		X[n]	X		
Tanner Staging (for subjects >7 to 18 years old)	X[a]			X[j]	X		
C-SSRS	X[a]			X	X		
CGI-I (assessed by parent/caregiver)	X[a]			X	X		
CGI-I (assessed by Principal Investigator)	X[a]			X	X		
HADS (Effect of parent/caregiver)	X[a]			X[o]	X		
BRIEF	X[a]			X[o]	X		
~~VABS~~	~~X[a]~~			~~X[a]~~	~~X~~		
QOLCE	X[a]			X[o]	X		
Zarit Burden	X[a]				X		
Subject Diary	C/R/D	C/R/D	R	C/R/D	C/R/D	C/R	
Study Medication	D	C/R	R	C/R/D	C/R/D[k]	C/R	
Review Daily Diary Completion	---------- X ----------						
Concomitant Medication	X[a]	----------X----------					
Adverse Events	X[a]	----------X----------					
Adverse events of special interest	X[a]	----------X----------					X[l]

Abbreviations: AED=antiepileptic drug; BMI=body mass index; C=Collect; CBD=cannabidiol; D=Dispense; ECG=electrocardiogram; 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~~

Sections 6.2.1, 6.2.3, 6.2.4

- ~~VABS (Appendix 4)~~

2. Update to IP temperature excursions in Section 5.3

5.3. SHIPMENT AND STORAGE

IMP will be supplied to the study sites by the Sponsor or its delegate.

All IMP will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions supplied to the research site and its designated pharmacy, the site's standard operating procedures, and applicable regulations. IMP must be stored separately from normal hospital or practice inventories, in a locked facility with access limited to the Investigator and authorized personnel. The Investigator must ensure that the IMP is dispensed only to subjects enrolled in this study according to this study protocol.

Appropriate storage temperature and transportation conditions will be maintained for the study drug from the point of manufacture up to delivery of the study drug. Study medication must be stored at 15 to 25°C (59 to 77°F) with excursions of 5 to ~~30~~40°C (41 to ~~86~~104°F) permitted; do not refrigerate or freeze.

3. Updates to Background information regarding existing treatments, new clinical data, and new pre-clinical data

Section 1.1.1: updated information about approved AEDs

Currently, there are 7 approved anti-epileptic drug (AED) products for LGS in the US: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, and cannabidiol (Epidiolex®). Two AEDs are approved in Japan for the treatment of LGS: lamotrigine (2008) and rufinamide (2013). ~~Eight~~ Nine AEDs are approved for the treatment of LGS in Europe: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, valproate, ~~and~~ nitrazepam, and cannabidiol (Epidyolex®). Other pharmacologic (valproate, benzodiazepines, zonisamide) and nonpharmacologic (KD, VNS, surgery) treatments also are prescribed based on clinical experience.

Section 1.3: new information from Phase 3 study results

In an integrated analysis of safety of the double-blind studies, 117 (95.9%) subjects in any ZX008 treatment group and 68 (81.0%) subjects in the combined placebo group reported at least 1 TEAE. Fifteen (12.3%) subjects in any ZX008 treatment group and 11 (13.1%) subjects in the combined placebo group reported at least 1 serious TEAE. A total of 76 (62.3%) subjects in any ZX008 treatment group and 22 (26.2%) subjects in the combined placebo group reported a TEAE determined by the Investigators to be related to the study drug, and 3 (2.5%) subjects in any ZX008 treatment group and 1 (1.2%) subject in the combined placebo group reported a serious TEAE determined to be related to the study drug. During the double-blind treatment periods, 7 (5.7%) subjects in any ZX008 treatment group and 1 (1.2%) subject in the combined placebo group reported a TEAE that lead to discontinuation from study participation. There were no deaths during the double-blind treatment periods.

Subjects in Study 1 and Study 1504 if eligible could participate in Study 1503, an open-label long-term, safety extension study that is currently ongoing. All subjects in Study 1503 started ZX008 at 0.2 mg/kg/day and could flexibly titrate to a maximum dose of 0.8 mg/kg/day, maximum 30 mg/day (if not receiving a concomitant STP regimen) or 0.5 mg/kg/day, maximum 20 mg/day (if receiving concomitant STP regimen), based on effectiveness, safety and tolerability. Though primarily a safety study, subjects in Study 1503 maintained a daily seizure diary and continued to complete rating scales on overall effectiveness and quality of life measures.

In a safety update of Study 1503 (cut-off date 14-Oct-2019, n=330 enrolled), the median percent change in CSF compared to baseline (core study) for the overall open-label Treatment period (Day 1 to End of Study [EOS]) was -66.8% (P <0.001). The reduction from baseline in monthly CSF observed at Month 1 of the open-label Treatment period was maintained through Month 24, the longest treatment duration included in the analysis. A total of 317/330 subjects reported at least 1 TEAE during the open-label Treatment period. The most common (≥ 10%) TEAEs reported during the open-label Study 1503 at the time of the cut-off date were blood glucose decreased, decreased appetite, diarrhea, ear infection, echocardiogram abnormal, influenza, nasopharyngitis, pyrexia, seizure, and upper respiratory tract infection. As in the double-blind studies, all of the echocardiogram abnormal TEAEs in Study 1503 were trace mitral or trace aortic valve regurgitation, which are not considered pathologic as stated in current guidelines on the use of ECHO for the assessment of valve function (Zoghbi 2017, Lancellotti 2010a, Lancellotti 2010b). At least 1 treatment-emergent SAE was reported by 80/330 (24.2%) subjects. The most frequently reported (≥ 5%) SAE was seizure occurring in 24/330 (7.3%) of subjects. A total of 176/330 subjects (53.3%) experienced at least 1 TEAE that was considered to be related to study treatment and 8/330 subjects (2.4%) reported at least 1 SAE that was considered to be related to study treatment. A total of 11/330 (3.3%) subjects discontinued due to a TEAE.

Please reference the ZX008 IB V.8 for more detailed information on the safety and efficacy of ZX008.

Section 1.4: additional preclinical and clinical pharmacology data; revision of subheadings for organization

1.4. . PHARMACOKINETICS, PRECLINICAL DATA, AND CLINICAL PHARMACOLOGY

1.4.1. Pharmacokinetics

The pharmacokinetics of fenfluramine, norfenfluramine and their respective isomers have been studied in mice, rats, dogs and humans. Fenfluramine and norfenfluramine were more slowly eliminated in humans than in other species. In vitro metabolism studies have shown considerable species differences in the metabolism of fenfluramine, with no single species having a profile similar to humans. No human-specific metabolites were detected, and both rat and dog showed good coverage of the human fenfluramine metabolites. In humans, fenfluramine is metabolized primarily to norfenfluramine. Fenfluramine is partially metabolized by CYP1A2, CYP2B6, and CYP2D6, with additional metabolism by CYP2C9, CYP2C19, and CYP3A4. Norfenfluramine does not appear to be strong substrate of any CYP450 enzyme, but is metabolized by CYP1A2, CYP2B6, CYP2C19, and CYP2D6 in vitro. There is also some contribution of renal clearance to the elimination of dexfenfluramine (8%-16%) and nordexfenflurmaine (7%-8%) from the body. Because fenfluramine and its active metabolite norfenfluramine have multiple pathways of elimination, interference with a single pathway is unlikely to cause a significant change in fenfluramine's clearance though the probability of an interaction increases if multiple elimination mechanisms are affected simultaneously.

While in vitro studies showed that both fenfluramine and norfenfluramine cause weak inhibition of CYP2D6 and fenfluramine causes weak induction of CYP3A4 and CYP2B6, further analysis based on the FDA's mechanistic static model shows that fenfluramine and its major metabolite norfenfluramine are unlikely to alter the pharmacokinetics of substrates of CYP450 enzymes in the range of ZX008 doses that will be administered in this study.

In Study 1 and Study 1504 Cohort 2, pharmacokinetic parameters of fenfluramine and norfenfluramine for patients with Dravet syndrome were determined using a population pharmacokinetic (PopPK) model developed using PK data from both healthy volunteers and patients with Dravet syndrome. These data are provided in Table 3.

Table 3: Post Hoc Estimates of Fenfluramine and Norfenfluramine Steady-State Pharmacokinetic Parameters in Subjects with Dravet Syndrome in Study 1 (Geometric Mean [CV%])

Analyte:	Fenfluramine		Norfenfluramine	
ZX008 Dose	0.2 mg/kg/day	0.8 mg/kg/day	0.2 mg/kg/day	0.8 mg/kg/day
C_{max} (ng/mL)	18.5 (29.1)	68.0 (40.7)	9.60 (52.8)	37.8 (49.9)
AUC_{0-24} (ng.hr/mL)	375 (32.9)	1390 (43.5)	220 (55.5)	872 (52.1)
T_{max} (hr) Median (Min, Max)	3.00 (3.00 to 3.50)	3.00 (3.00 to 3.50)	4.00 (3.50 to 5.00)	4.50 (3.50 to 5.00)

Source: ICPD Report 00445-3, Table 5.
Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours; BID = twice daily; C_{max} = peak plasma drug concentration; CV= coefficient of variation; Max = maximum; Min = minimum; T_{max} = time of peak plasma drug concentration.

1.4.2. Preclinical Data

In a GLP compliant 10-week juvenile toxicology and toxicokinetic study in rats, which included fenfluramine hydrochloride doses of 3.5, 9 and 20 mg/kg/day by oral gavage for 10 weeks (Days 7 to 76 postpartum). The data from the juvenile toxicology studies suggest that the effects of fenfluramine in juvenile animals (CNS-related clinical signs, effects on body weight and food consumption, and neurobehavioral deficits) are similar to effects previously reported in neonatal and adult rats (Morford 2002; Williams 2002). There was no evidence of CNS histopathology; importantly, there were also no histopathologic findings in aortic or mitral cardiac valves, and no adverse effects on any other tissues at necropsy.

The NOAEL for the juvenile rats was determined to be 9 mg/kg/day. A NOAEL of 9 mg/kg/day corresponds to PND 76 AUC0-t of 3480 hr*ng/mL for males and 4680 hr*ng/mL for females for fenfluramine, and 4470 hr*ng/mL for males and 6210 hr*ng/mL for females for norfenfluramine. The AUC(0-t) at the NOAEL provided a safety factor (both sexes combined) of approximately 3-fold or higher for fenfluramine and approximately 6-fold or higher for norfenfluramine.

1.4.3. Clinical Pharmacology

Please see the ZX008 IB for details on clinical pharmacology. Below are the clinical pharmacology conclusions.

- Coadministration of ZX008 with the STP regimen (STP with CLB and/or VPA) resulted in an increased fenfluramine and decreased norfenfluramine concentrations, and therefore a dose adjustment is used in the clinical trials.
- STP is the predominant perpetrator of the interaction; while VPA and CLB do not have a significant independent impact on the PK of fenfluramine or norfenfluramine, whether administered with or without STP.
- Coadministration of ZX008 with CBD at steady state resulted in increased fenfluramine concentrations but this increase was within the range of safe dosing used in Study 1504 Cohort 2; thus, no dose adjustment is recommended when fenfluramine is coadministered with CBD.
- In the population PK analysis, intrinsic patient factors (age, gender, race/ethnicity, and BMI) demonstrated no substantial impact on the clearance or exposure to fenfluramine or norfenfluramine when dosed on a mg/kg basis to a maximum of 30 mg/day.
- ZX008 had no effect on QTc intervals at either the therapeutic or supratherapeutic dose, and no relationship was observed between fenfluramine or norfenfluramine exposure and QTcF.
- ZX008 exhibited approximately dose proportional PK over a 4-fold range of doses (15 to 120 mg/day).
- CYP450 metabolizer genotype for CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 had no impact on the PK of fenfluramine or norfenfluramine.

~~The LOAEL of 3.5 mg/kg/day is associated with an $AUC_{(0-t)}$ of 662 ng*h/mL (male rats) or 764 ng*h/mL (female rats) on post natal day (PND)76 for fenfluramine. For norfenfluramine, this dose is associated with an $AUC_{(0-t)}$ of 1930 ng*h/mL (male rats) or 2400 ng*h/mL (female rats) on PND76. In comparison, the predicted AUC(0-t) for pediatric patients between the ages of 2 and 18 years, at the highest dose of 30 mg/day, is 1323 ng*h/mL for fenfluramine and 711 ng*h/mL for norfenfluramine.~~ Further details on the nonclinical data of ZX008 are available in the Investigator's Brochure (ZX008 IB ~~2018 V6.0~~). The current version is available in the Investigator Study File.

4. Minor clarification in Section 5.5.6, for consistency with Section 6.2.1

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

5. Information and instruction added for COVID-19 in Section 6.3 and Appendix 9

New Section 6.3

6.3. STUDY CONDUCT DURING COVID-19

In March 2020, the World Health Organization declared a global pandemic related to an illness caused by a novel coronavirus known as COVID-19. Alternative procedures and allowances are permitted due to restrictions related to COVID-19, including delays to in-person visits and specific assessments, performing remote phone or video visits if in-person visits cannot be conducted, and arranging shipments of investigational product directly to subjects. These allowances are detailed in Appendix 10. Though every attempt should be made to conduct study visits as described in this protocol, any implementation of alternative processes should be properly documented, including what was done differently, which assessments or visits were missed or performed via phone or video.

New Appendix 9, which provides study conduct information during the COVID-19 Pandemic

APPENDIX 10 – STUDY CONDUCT DURING COVID-19

In March 2020, the World Health Organization declared a global pandemic related to an illness caused by a novel coronavirus known as COVID-19. As a result, public health initiatives, such as laws, regulations and policies were enacted at country and institutional levels to protect the health of the general public. These initiatives and policies have affected the ability of study sites to conduct the trial per protocol and the ability of the sponsor and/or delegate to conduct trial oversight and monitoring visits.
In an effort to support the rights, safety and welfare of subjects and ensure as little impact on the integrity of the research as possible the following alternative processes have been implemented due to restrictions related to COVID-19. Though every attempt should be made to conduct study visits per protocol, any implementation of alternative processes should be properly documented.