CLINICAL STUDY PROTOCOL

Study Title:	An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome
Study Number:	ZX008-1900/EP0215
Study Product:	Fenfluramine Hydrochloride Oral Solution; ZX008
IND Number:	125797, 132604
EudraCT:	2019-001331-31
Sponsor:	Zogenix International Limited an indirectly wholly owned subsidiary of Zogenix Inc. which is a directly wholly owned subsidiary of UCB Biosciences, 4000 Paramount Pkwy, Suite 200, Morrisville, NC 27560, USA
Sponsor's Medical Contact	[redacted] Study Physician UCB Biosciences Inc
Date/Version of Study Protocol:	22 September 2022 (Amendment 4.0) 27 July 2020 (Amendment 3.1) 13 July 2020 (Amendment 3.0) 04 Sep 2019 (Amendment 2.2) 11 July 2019 (Amendment 2.0) 22 April 2019 (Amendment 1.0) 1 March 2019 (Original)

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.

TABLE OF CONTENTS

TABLE OF CONTENTS....2
LIST OF TABLES....5
SIGNATURE OF SPONSOR....6
SIGNATURES OF COORDINATING INVESTIGATOR....7
SIGNATURE(S) OF PRINCIPAL INVESTIGATOR(S)....8
LIST OF ABBREVIATIONS....9
STUDY SYNOPSIS....11
1. INTRODUCTION....18
1.1. Background Information on Indication Studied....18
1.2. Background Information on Study Product....20
1.3. Preclinical Data....20
1.4. Clinical Pharmacology....21
1.5. Clinical Data....22
1.6. Rationale for Current Study....25
2. STUDY OBJECTIVES AND ENDPOINTS....27
2.1. Primary Objective....27
2.2. Secondary Objectives....27
2.3. Study Endpoints....27
3. INVESTIGATIONAL PLAN....29
3.1. Overall Study Design and Plan....29
3.2. Number of Subjects....30
3.3. Study Duration....30
3.4. Number of Study Centers....30
3.5. Rationale for Study Design....30
3.6. Premature Termination of Study....31
3.7. Study Monitoring Procedures....31
4. SELECTION OF STUDY POPULATION....33
4.1. Inclusion Criteria....33
4.2. Exclusion Criteria....33
4.3. Subjects of Reproductive Potential....34
4.4. Removal of Subjects from Therapy or Assessment....36

4.5. Termination of the Clinical Study 38
4.6. Replacement of Subjects....38
5. INVESTIGATIONAL MEDICINAL PRODUCT INFORMATION 39
5.1. Identity of Investigational Medicinal Product 39
5.2. Shipment and Storage 39
5.3. Investigational Medicinal Product Accountability 40
5.4. Treatment Administration....40
5.5. Blinding 42
5.6. Prior and Concomitant Medication....42
5.7. Treatment Compliance....44
6. VISIT SCHEDULE 45
6.1. Open-label Extension Treatment Period....45
6.2. EOS/ET Follow Up Visit (Clinic Visit 8; EOS/ET +14 days) 49
6.3. Cardiac Follow Up Visit (Clinic Visit 9; last dose + 6 Months) 49
6.4. Estimated Blood Volume Collection 50
6.5. Specific guidance related to COVID-19 pandemic 51
7. EFFECTIVENESS, SAFETY, AND PHARMACOKINETIC ASSESSMENTS....52
7.1. Effectiveness Assessments 52
7.2. Safety Assessments....53
7.3. Appropriateness of Measurements 56
8. ADVERSE EVENTS....57
8.1. Definitions....57
8.2. Severity of Adverse Events 59
8.3. Causality of Adverse Events....59
8.4. Observation Period for Adverse Event Reporting 60
8.5. Adverse Event Reporting....60
8.6. Serious Adverse Events Reporting 61
8.7. Reporting of Serious Adverse Events by Investigator to IEC/IRB 62
8.8. Reporting of Events Other Than Serious Adverse Events by Investigator to Sponsor 62
8.9. Follow-up of Adverse Events 62
8.10. Pregnancy 65

9. DATA HANDLING PROCEDURES 66
9.1. Recording of Data 66
9.2. Data Quality Assurance 66
9.3. Record Retention 66
10. STATISTICS 68
10.1. Determination of Sample Size 68
10.2. Analysis Populations 68
10.3. Treatment Groups 68
10.4. Treatment Periods 68
10.5. Statistical Analyses and Methods 69
10.6. Analyses Provided to an Independent Data and Safety Monitoring Committee 70
11. ETHICAL & REGULATORY CONSIDERATIONS 71
11.1. Ethical Considerations 71
11.2. Informed Consent 71
11.3. Regulatory Considerations and Independent Ethics Committee/Institutional Review Board 72
11.4. Protocol Compliance 73
12. ADMINISTRATIVE ASPECTS 74
12.1. Clinical Trial Agreement 74
12.2. Financial Disclosure by Investigator 74
12.3. Clinical Study Registration and Results Disclosure 74
12.4. Study Files and Materials 74
12.5. Initiation of the Study 75
12.6. Subject Reimbursement 75
12.7. Liability and Insurance 75
12.8. Subject Identification and Confidentiality 75
12.9. Monitoring of the Study 76
12.10. Protocol Amendments 77
12.11. Audits and Inspections 77
12.12. Clinical Study Report 77
12.13. Use of Data and Publications 78
13. REFERENCE LIST 79

14. APPENDICES 82
14.1. Appendix 1 – List of Restricted Concomitant Medications 82
14.2. Appendix 2 – Columbia – Suicide Severity Rating Scale 83
14.3. Appendix 3 – Clinical Global Impression – Severity (CGI-S) 86
14.4. Appendix 4 – Clinical Global Impression – Improvement (CGI-I) 88
14.5. Appendix 5 – Maximum Allowable Blood Draw Volumes 90
14.6. Appendix 6 - Study Conduct During COVID-19 91
14.7. Appendix 7- Summary of Protocol Amendment 3.0 94

LIST OF TABLES

Table 1. Schedule of Assessments for Subjects 15
Table 2. Investigational Medicinal Product – ZX008 39
Table 3. Taper Algorithm 42
Table 4. Time Windows for Assessments 45
Table 5. Schedule of Post-Treatment Cardiac Follow-up 50
Table 6. Estimated Blood Volume Collection[a] 50
Table 7. Severity Definition of Adverse Events[a] 59
Table 8. Clinical Measures Enacted Upon Increasing Severity of ECHO Findings 63

SIGNATURE OF SPONSOR

Study Number: ZX008-1900

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome

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[redacted] 03-oct.-2022

(Signature) (Date [DD/MMM/YYYY])

On behalf of [redacted]:

[redacted]
UCB Biosciences Inc.

SIGNATURES OF COORDINATING INVESTIGATOR

Study Number: ZX008-1900/EP0215

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome

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Co-Coordinating Investigator: [redacted]

University of California, San Francisco
San Francisco, CA USA

_____ _____
(Signature) (Date [DD/MMM/YYYY])

SIGNATURE(S) OF PRINCIPAL INVESTIGATOR(S)

Study Number: *ZX008-1900/EP0215*

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome

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 and affiliation: _____

_____

_____ _____

(Signature) (Date [DD/MMM/YYYY])

LIST OF ABBREVIATIONS

ABBREVATION	DEFINITION
AE	adverse event
AED	antiepileptic drug
ANCOVA	analysis of covariance
AS	atonic seizure
BID	bis in die; 2 times per day
BMI	body mass index
CBD	cannabidiol
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement
CRO	Contract Research Organization
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
dL	deciliter
ECG	electrocardiogram
ECHO	echocardiogram
EOS	end of study
ET	early termination
FS	focal seizure
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GH	growth hormone
GTC	Generalized Tonic Clonic (seizure)
GMP	Good Manufacturing Practices
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
ICF	informed consent form
ICH	International Conference on Harmonization
IDSMC	Independent Data and Safety Monitoring Committee
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IMP	investigational medicinal product
ICAB	International Cardiology Advisory Board
IRB	Institutional Review Board
IWR	interactive web response (system)
KD	ketogenic diet
kg	kilogram

ABBREVATION	DEFINITION
LGS	*Lennox-Gastaut syndrome*
LH	luteinizing hormone
LLN	lower limit of normal
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
OLE	open-label extension
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SE	status epilepticus
SMEI	severe myoclonic epilepsy of infancy
SoA	schedule of assessments
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy
TEAE	Treatment Emergent Adverse Event
THC	tetrahydrocannabinol
TS	tonic seizure
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
USP	United States Pharmacopeia
VNS	vagal nerve stimulator/stimulation
ZX008	fenfluramine hydrochloride oral solution

STUDY SYNOPSIS

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome	
Study Number: ZX008-1900	
Study Product: Fenfluramine Hydrochloride Oral Solution, ZX008	
Type of Study: Long-term safety	**Indication(s) Studied:** Rare Seizure Disorders Such as Epileptic Encephalopathies, including Dravet syndrome and Lennox-Gastaut syndrome
Phase of Development: Phase III	**Countries:** North America, Europe, Australia, and Japan
Sponsor: Zogenix International Limited	
Co-Coordinating Investigator: [redacted]	
Estimated Duration of Individual Subject Participation: Participation for subjects will be voluntary until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects' country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first.	
Objectives: The primary objective of the study is: • To assess the long-term safety and tolerability of ZX008 The secondary objectives of the study are: • To assess the effect of ZX008 on the following effectiveness measures: – Investigator assessment of convulsive seizure response (<25%, ≥25%, ≥50%, ≥75%, or 100% [ie, seizure-free] improvement) – Clinical Global Impression – Improvement (CGI-I) rating, global and symptomatic, as assessed by the investigator – CGI-I rating, global and symptomatic, as assessed by the parent/caregiver	
Methodology: This is an international, multicenter, open-label, long-term safety study of ZX008 in patients with rare seizure disorders, epileptic encephalopathy, including Dravet syndrome or Lennox-Gastaut syndrome. Subjects eligible for participation are those with Dravet syndrome who are currently enrolled in Study ZX008-1503, or those with LGS who have successfully completed Study ZX008-1601-Part 2, and are candidates for continued treatment with ZX008 for an extended period of time, or those with Dravet syndrome, Lennox-Gastaut syndrome, or another epileptic encephalopathy who have completed participation in a Zogenix-sponsored study and have been invited to participate in this study. Participation in this OLE study is entirely voluntary. Subject will be eligible to participate in this trial until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first. Subjects entering this OLE study who have participated in 1503 or 1601 will receive ZX008 initially at the dose prescribed at the last visit in Study 1503 or Study 1601 Part 2, but will have the volume adjusted according to weight of the patient. Dose increases, to a maximum of 0.8 mg/kg/day (maximum 30 mg/day) for subjects not receiving concomitant stiripentol (STP) or 0.5 mg/kg/day (maximum 20 mg/day) for subjects receiving concomitant stiripentol (STP), during this OLE study should not occur more frequently than	

every 7 days in dose increments of not more than 0.2 mg/kg/day. Dose increases may only occur after a review of reported adverse events (AEs), and if, in the investigator's opinion, seizure frequency, severity, or duration indicates a change in medication regimen is warranted. Dose decreases for tolerability or safety concerns can occur at the investigator's discretion, in dose amounts and frequency appropriate for the clinical situation. ZX008 dose adjustments outside of these parameters should be discussed with the Contract Research Organization (CRO) Medical Monitor prior to initiation.

Changes in dosage of concomitant AEDs may be implemented as clinically necessary, and concomitant AEDs may be withdrawn completely, but all subjects must remain on a minimum of 1 concomitant AED plus ZX008 unless it is deemed clinically appropriate by the investigator (after discussion with the CRO Medical Monitor) to dose as monotherapy. New concomitant AEDs or anti-epileptic treatments may be introduced at the investigator's discretion, as would be typically indicated in clinical practice. Clinical worsening leading to a change in medication must be documented in the source notes and case report form (CRF) and all medication dose changes must be documented with a clinical explanation and justification. Any addition of a new AED must be discussed with the CRO Medical Monitor prior to implementation.

Echocardiograms (ECHO) and other safety assessments detailed in the schedule of assessments (SoA) will be conducted every 6 months unless more frequent follow-up is clinically indicated or required by the Sponsor or IDSMC. A Follow-up visit and a cardiac safety assessment will be performed after study drug discontinuation for subjects who do not transition to commercially available ZX008. Subjects who transition to commercially available ZX008 will not return for a follow-up after EOS/ET or a cardiac follow up after last dose but must have had an ECHO within 3 to 6 months before the transition date and will have follow-up ECHOs within required timeframe while on commercial drug supply.

Caregivers will be asked to use a diary to record the number/type of seizures to support investigator determination of treatment benefit; however, diary data collection is not mandatory, nor will it be collected in the database. A schedule of assessments is provided in Table 1.

External Committees: The ZX008 clinical program will employ an Independent Data and Safety Monitoring Committee (IDSMC) that will be responsible for safety oversight until the safety oversight is transferred back to the Sponsor or the drug is approved in a major market for the studied indications. A separate International Cardiology Advisory Board (ICAB) will monitor the cardiac safety of the ZX008 clinical trials. ECHOs will be centrally read (ERT, Inc.) and interpreted using pre-specified criteria, and if necessary, with review by the ICAB.

Number of Subjects: Up to approximately 650 subjects from the core studies may be enrolled.

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

1. Subject is currently enrolled in core Study ZX008-1503

   OR

   Subject has successfully completed core Study ZX008-1601-Part 2

   OR

   Subject with a rare seizure disorder, such as epileptic encephalopathy, that has successfully completed another Zogenix-sponsored clinical trial with ZX008, and has been invited to participate in this study by the Sponsor.
2. Subjects must, in the medical opinion of the Investigator, be candidates for continued treatment for an extended period of time with ZX008 (ie, subject has demonstrated a clinically meaningful benefit with ZX008 in the prior trial, and benefits of continued treatment outweigh potential risks).
3. Subject is male or a nonpregnant, nonlactating female. Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative pregnancy test prior to study entry. Subjects of childbearing or child-fathering potential must be willing to use medically acceptable forms of birth control, which includes abstinence, while being treated on this study and for 90 days after the last dose of study drug.
4. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.

5. Subject has provided assent in accordance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements, if capable.
6. Subject's caregiver is willing and able to be compliant with study procedures, visit schedule and study drug accountability.

Exclusion Criteria: All subjects must meet none of the following exclusion criteria to be enrolled into the study:

1. Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication.
2. Subject has current cardiac valvulopathy or pulmonary hypertension that the investigator, ICAB, IDSMC, or Sponsor deems reason for exclusion.
3. 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 as measured by the C-SSRS Since Last Visit, 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.
4. Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x upper limit of normal [ULN] and/or elevated bilirubin < 2x ULN) may be entered into the study after review and approval by the CRO Medical Monitor in conjunction with the Sponsor, in consideration of comorbidities and concomitant medications.
5. Administration of a prohibited medication (see section 5.6.2) within 14 days of receiving ZX008.
6. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
7. Subject has a clinically significant condition, or has had clinically relevant symptoms or a clinically significant illness at Visit 1, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject, including chronic obstructive pulmonary disease, interstitial lung disease, or portal hypertension.
8. Subject has participated in another clinical treatment trial within the past 30 days (ie, the last visit of the previous study was in the past 30 days), with the exception of a ZX008 clinical study.

Reference Product, Dose, and Mode of Administration:

Not applicable.

Duration of Treatment:

All subjects will receive ZX008 until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first. All subjects who discontinue from the study treatment and do not transition directly to commercial product will undergo up to 2-weeks taper of study medication.

Criteria for Evaluation:

Safety:

AEs, vital signs (blood pressure, heart rate, temperature, and respiratory rate), physical examination, neurological examination, Doppler ECHOs, and body height/weight will be assessed at each visit. Laboratory safety parameters (hematology, chemistry), 12 -lead ECGs, EEGs (in Italy only), and chest-x-ray (in France and Netherlands only), will be assessed as clinically indicated.

Effectiveness (assessed at each visit):

- CGI-I global and for cognition, behavior, motor abilities, as assessed by parent/caregiver
- CGI-I global and for cognition, behavior, motor abilities, as assessed by investigator (or designee)

- Percent improvement in seizure burden as assessed by the investigator (or designee)

Assessments by the investigator (or designee) should be performed by the same rater for each subject whenever possible. If the rater changes permanently, a new baseline CGI-S (Appendix 3) should be established (see Section 7.1).

The same parent/caregiver should perform each assessment. If the same parent/caregiver is not available, the assessment should be skipped.

Sample Size Determination:

The sample size will be determined by the number of subjects who participate in Study ZX008-1503 or ZX008-1601 Part 2 and who volunteer for the extension study and meet the necessary criteria for enrollment.

Statistical Methods:

Study Populations

Safety Population: Safety analyses will be performed on the Safety Population defined as all subjects who receive at least 1 dose of ZX008 during this study.

Safety

The number and percentage of subjects who experience treatment emergent AEs will be displayed by System Organ Class (SOC) 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. Serious AEs (SAEs) will be summarized separately in a similar manner. Vital signs, physical examinations, neurological examinations, ECHO, and body height/weight will be summarized using appropriate methods. Abnormal findings on clinical laboratories, ECGs, EEGs, and chest x-rays that are recorded as adverse events will be summarized.

Effectiveness

The treating physician (or designee) will rate their global impression of the severity of the subject's condition at Visit 1 to establish a reference baseline CGI-S (appendix 3), and then at each visit with the CGI-I throughout treatment with ZX008 according to the Schedule of Assessments. The severity of a subject's condition will be rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) by indicating the appropriate response that adequately describes how the subject's symptoms have improved or worsened relative to the reference baseline. The CGI-I will also be completed by the parent/caregiver. The mean (SD) CGI-I score, and the number and percentage of subjects who showed improvement (ie, had a score of 3 or lower), or clinically meaningful improvement (i.e., had a score of 2 or lower) will be presented for each assessment timepoint. Global CGI-I score and CGI-I score for cognition, behavior and motor abilities will be summarized and analyzed using the same methods, as described above. Investigators will also rate overall change in convulsive seizure frequency as <25%, ≥25%, ≥50%, ≥75%, or 100% (ie, seizure-free) improvement compared to last visit.

Table 1. Schedule of Assessments for Subjects

Study Assessments		**OLE Treatment Period***		**Follow-up**	**Cardiac Follow-up**
Visit Number	**Visit 1[a]**	**Visits 2, 3, 4, 5, 6 (Months 6, 12, 18, 24, 30)**	**Visit 7 (EOS/ET) Month 36**	**Visit 8 EOS/ET+ 14 days**	**Visit 9[h] last dose + 6 months**
Study Day	**1[a]**	**180, 360, 540, 720, 900 (window: ±7 days)**	**1080 (window: ±7 days)**	**14 days after EOS/ET**	**6 months post last dose**
Informed Consent	X[a]				
Entry Criteria Review	X				
Demographics	X				
Epilepsy History	X				
Abbreviated Physical/Neurological Examination	X[b]	X[f]	X	X[m]	X
Vital signs	X	X	X		
Weight, Height, BMI	X	X	X	X	
ECG[b,c]	X	X	X		X
Doppler ECHO[d]	X	X	X		X
Chest X-ray (France and Netherlands only)[b, e]	X	X	X		X
EEG (Italy only)[b, c,i]	X	X	X		
Pregnancy Test[g]	X	X	X		
Clinical laboratory evaluation (hematology/clinical chemistry)	X[b]	X[f]	X[f]		
Plasma sample for background AEDs		X[f]	X[f]		
C-SSRS	X	X	X		
Investigator CGI-Severity Rating (reference baseline)	X				

Parent/Caregiver CGI-Severity Rating (reference baseline)	X				
CGI-I (assessed by parent/caregiver)		X	X		
CGI-I (assessed by investigator)		X	X		
Overall change in seizure frequency (assessed by investigator)	X	X	X		
Study Medication	D	C/R/D[k]	C/R/D	C/R	
Seizure Diary	R (if applicable)[l]	R (if applicable)	R (if applicable)		
Concomitant Medications	X[j]	X	----------X----------		
Adverse Events	X[j]	X	----------X----------		

BMI=body mass index; C=Collect; CGI-I=Clinical Global Impression-Improvement; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination; R=Review

*: Subjects will receive ZX008 treatment in this study until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subject's country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first. In that regard, participation could be extended beyond 36 months if none of the conditions above mentioned are met.

a: Assessments conducted at the End of Study Visit of 1503, 1601 Part 2, or other Zogenix protocol as applicable will be used for Visit 1 of this Protocol. Continuation of treatment in this study should be discussed at the start of the visit, at latest. For subjects who wish to continue, informed consent/assent must be obtained before conducting any assessments or distributing study drug under this protocol.

b: As clinically indicated based on medical history, and/or signs/symptoms. Abnormal clinically significant findings must be reported as adverse events.

c: Conducted and read locally. Abnormal clinically significant observations must be reported as adverse events.

d: ECHO will be performed every 6 months, starting with Visit 1, unless more frequent ECHO is clinically indicated.

e: In France and Netherlands only. Subjects in France and Netherlands will have an additional Chest X-ray 24 months after study completion.

f: As clinically indicated. A full physical and/or neurological examination may be performed, if warranted. Abnormal clinically significant observations must be reported as adverse events.

g: Females of child-bearing potential

h: For subjects who do not continue with commercially available ZX008, a follow up will be performed 14 days after study completion or early termination and a follow-up ECHO, and physical examination will be performed 6 months after last dose. Subjects in the United Kingdom will have an additional follow-up 12 months after study completion; subjects in France, Germany, and Netherlands will have an additional follow-up 24 months after study completion.

i: In Italy only.

j: Ongoing medications and ongoing adverse events should be captured in the CRF.

k: At the Principal Investigators discretion Study Drug can be collected/reviewed/dispensed at 3 month intervals.
l: Seizure Diary from core study to be reviewed, if applicable.
m: As appropriate based on last exam and reported AEs

1. INTRODUCTION

1.1. Background Information on Indication Studied

ZX008 (fenfluramine hydrochloride) is under development for the adjunctive treatment of patients with Dravet syndrome and Lennox-Gastaut syndrome. Fenfluramine (Fintepla®) is authorized for sale in the United States for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

An epileptic encephalopathy is "a condition in which the epileptic activity itself may directly contribute additional cognitive and behavioral impairments over those expected from the underlying etiology alone and that suppression of epileptic activity might minimize this additional impairment" (Scheffer 2017).

Future development plans for ZX008 may include other rare epilepsy disorders and other epileptic encephalopathies.

About Dravet Syndrome

Dravet syndrome is a rare and severe form of epilepsy first described by Charlotte Dravet in 1978 (Dravet 1978). The condition most commonly appears during the first year of life as frequent febrile seizures. As the condition progresses, other types of seizures typically occur, including myoclonic seizures and status epilepticus (SE) (Dravet 1978). Following the appearance of these seizures, affected children develop several co-morbid conditions including psychomotor regression, ataxia, sleep disturbance, and cognitive impairment. Intellectual impairment begins to become apparent around age 2 years due to lack of intellectual/behavioral progression. Children with Dravet syndrome often have a lack of coordination, poor development of language, hyperactivity, and difficulty relating to others (Dravet 1978; Hurst 1990). The degree of cognitive impairment appears to correlate, at least in part, with the frequency of seizures, and might be a result of repeated cerebral hypoxia. Children with Dravet syndrome also encounter a higher incidence of sudden unexpected death in epilepsy (SUDEP; Nashef 2012) than other populations with epilepsy. Indirect evidence has linked SUDEP to several possible etiologies, including seizure-induced apnea, pulmonary edema, dysregulation of cerebral circulation, and cardiac arrhythmias (Shorvon 2011), although the actual etiology remains unknown and other mechanisms have not been ruled out. The vast majority of patients who survive to adulthood are wholly dependent on around-the-clock caregivers and eventually live in institutional care homes.

About Lennox-Gastaut Syndrome

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 to 10% of children with seizures (Panayiotopoulos 2005). The diagnosis of LGS includes clinical signs combined with typical electroencephalograph (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, 80–90% 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 Dravet Syndrome

Diacomit® (stiripentol) was recently approved in the United States, and has been approved for many years in Canada, Europe, and Japan to treat seizures associated with Dravet syndrome. Stiripentol (STP) must be co-administered with clobazam (US label) or clobazam and valproate (ex-US label). STP can significantly impact plasma concentrations of other AEDs, most notably clobazam. The complex drug-drug interactions of STP with other medications requires close monitoring and close management of side effects.

Fintepla® and Epidiolex® (cannabidiol) has recently been approved by the FDA and EMA (Fintepla®, Epidyolex®) for the treatment of seizures associated with Dravet syndrome.

Other therapies, topiramate, levetiracetam, and bromide may provide efficacy as adjunctive therapy for some patients (Chiron 2011). Published uncontrolled studies with levetiracetam (Striano 2007), verapamil (Iannetti 2009), ketogenic diet (KD) (Caraballo 2011a; Caraballo 2011b), deep brain stimulation (Andrade 2010), and vagal nerve stimulation (VNS) (Zamponi 2011) show infrequent clinically meaningful improvement. Carbamazepine, oxcarbazepine, lamotrigine, phenytoin, vigabatrin, and high doses of intravenous phenobarbital should be avoided because they often exacerbate seizures (Sazgar 2005; Wirrell 2016; de Lange 2018). Rescue medications (clonazepam, diazepam, lorazepam, and midazolam, etc) are often used to stop prolonged seizures that may evolve to SE and require emergency intervention.

1.1.2. Existing Treatment for Lennox-Gastaut Syndrome

Currently, there are 8 approved anti-epileptic drug (AED) products for LGS in the US: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, cannabidiol (Epidiolex®) and fenfluramine (Fintepla®). 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) and seizures in LGS are usually not fully controlled (Hancock 2013). Initial treatment for LGS is usually monotherapy with 1 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 each 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.

1.2. Background Information on Study Product

Zogenix is developing ZX008, an oral solution of fenfluramine hydrochloride, for the treatment of seizures associated with Dravet syndrome and for the treatment of seizures associated Lennox-Gastaut syndrome. Fenfluramine is a racemic compound containing dexfenfluramine and levofenfluramine. The stereochemical configuration of the d or (+) isomer (also known as dexfenfluramine or dextrofenfluramine) corresponds to the S enantiomer, and the configuration of the l or (-) isomer (levofenfluramine) corresponds to the R enantiomer. The active pharmaceutical ingredient (API) in the ZX008 drug product is fenfluramine hydrochloride.

Fenfluramine was approved in Europe in the 1960s, and in the United States (Pondimin NDA 16618) in the 1970s as an appetite suppressant at a dose of 60 to 120 mg/day for the treatment of adult obesity. Fenfluramine was also used extensively in an off-label combination with phentermine ("Fen-Phen"). The single enantiomer (+) fenfluramine (dexfenfluramine) was also approved and marketed as Adifax, Redux® (NDA 20-344), and others as an anorectic medication. Fenfluramine (racemate) was sold in 118 countries and was in clinical use for 20 to 30 years in France (1962), the Netherlands (1963), the United Kingdom (1966), Australia (1966), Spain (1966), Belgium (1966), South Africa (1968), Canada (1971, Germany (1972), Italy (1973), and the US (1973). Approximately 50 million Europeans were treated with fenfluramine for appetite suppression between 1963 and 1996 (Barceloux 2012) and the US Department of Health and Human Services estimated an exposure of over 61 million patient months prior to its global withdrawal in 1997 (CDC 1997).

Fenfluramine was withdrawn from world-wide markets in the late 1990s due to its association with cardiac valve abnormalities (CDC 1997; Connolly 1997; Wong 1998). Published case reports have also reported cases of primary pulmonary hypertension claiming to be associated with fenfluramine (Douglas 1981; McMurray 1986; Pouwels 1990; EMA 1999). The drug was not controlled where it was marketed, other than the United States, where it was classified as a Schedule IV drug under the Drug Enforcement Agency. A process was underway in the United States to propose the descheduling fenfluramine and its d(+) enantiomer, dexfenfluramine, immediately prior to their removal from the market (Federal Register 1997).

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 (ZX008 Investigator Brochure 2020). There is also a large body of information concerning its clinical safety profile.

1.3. Preclinical Data

The pharmacokinetics of fenfluramine, norfenfluramine and their respective isomers have been studied in mice, rats, dogs and humans. The PK in humans differs from that of other species,

with a longer duration of exposure to both the parent and the metabolite. In vitro metabolism studies have shown that there are large species differences in PK and metabolism of fenfluramine after oral administration.

Fenfluramine is metabolized to norfenfluramine. CYP1A2, CYP2B6 and CYP2D6 appear to be the predominant CYP (cytochrome P450) enzymes that metabolize fenfluramine to norfenfluramine. CYP2C9, CYP2C19 and CYP3A4 also appear to be involved, but to a lesser degree. 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 Food and Drug Administration's (FDA's) mechanistic static model shows that fenfluramine and its major metabolite norfenfluramine are unlikely to alter the PK of substrates of these CYP450 enzymes in the range of ZX008 doses that will be administered in this study.

A 10-week GLP 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 (ZX008 IB). There was no evidence of CNS-related histopathology findings.; 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 in this study, 9 mg/kg/day, provided a safety factor (both sexes combined) of approximately 3-fold or higher for fenfluramine and approximately 6-fold or higher for norfenfluramine.

Further details on the preclinical data of ZX008 are available in the Investigator's Brochure (ZX008 IB 2022 v10.0).

1.4. Clinical Pharmacology

Please see the ZX008 IB for details on clinical pharmacology (ZX008 IB 2022 v10.0). 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.

1.5. Clinical Data

1.5.1. Dravet Syndrome

Zogenix has conducted 2 positive, adequate and well-controlled, multi-national, randomized, double-blind, placebo-controlled trials of ZX008 in subjects with Dravet syndrome aged 2 to 18 years, Study 1 and Study 1504 Cohort 2. Study 1 compared 2 doses of ZX008, 0.8 mg/kg/day and 0.2 mg/kg/day, to placebo in subjects receiving standard of care anti-epileptic treatments excluding stiripentol (STP). Study 1504 Cohort 2 compared a dose of ZX008 0.5 mg/kg/day to placebo in subjects who were receiving stable standard of care anti-epileptic treatments where administration of STP (in combination with clobazam [CLB] and/or valproate [VPA]; ie, the STP regimen) was mandatory. These subjects were randomized to receive ZX008 or placebo in addition to their current standard of care treatments. The dose of 0.5 mg/kg/day was selected to account for the anticipated drug interaction when ZX008 was administered in combination with STP.

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) Treatment period. Key secondary objectives in both studies included a comparison of subjects who experienced at least a 50% reduction in monthly convulsive seizure frequency (also known as the ≥ 50% Responder Rate), and the median longest seizure free interval between convulsive seizures.

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frequency (also known as the ≥ 50% Responder Rate), and the median longest seizure free interval between convulsive seizures.

Both Study 1 and Study 1504 Cohort 2 met the primary efficacy endpoint and all key secondary efficacy endpoints. In Study 1, subjects randomized to ZX008 0.8 mg/kg/day achieved a reduction in mean monthly (28 days) baseline-adjusted CSF of 62.3% compared to placebo ($P < 0.001$) and subjects randomized to ZX008 0.2 mg/kg/day achieved a 32.4% reduction compared to placebo ($P = 0.021$). In Study 1504 Cohort 2, in which all subjects were taking STP, 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 ($P < 0.001$).

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 3 (2.5%) subjects in any ZX008 treatment group and 1 (1.2%) subject in the combined placebo group reported a serious TEAE determined by Investigators to be related to the study drug. In Study 1, two subjects, both of whom were in the ZX008 0.8 mg/kg/day group, reported SAEs that were considered by the Investigator to be related to study drug: SAEs of lethargy, and diarrhea leading to hospitalization in a 9-year old female who was discontinued from the study; SAEs of seizure leading to hospitalization, drowsiness, reduced appetite, and weight loss in a 3-year old male who was discontinued from the study (The

recorded weight loss was less than 1 kg.) In Study 1504 Cohort 2, two subjects reported SAEs that were considered by the Investigator to be related to study drug: 2 episodes of seizure cluster, and seizure leading to hospitalization in a 2-year old male in the placebo group; lethargy in a 7-year old female in the ZX008 0.5 mg/kg/day group who was discontinued from the study. 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 this study, Study 1503, an open-label long-term, safety extension study. 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 2022 v.10.0 for more detailed information on the safety and efficacy of ZX008.

1.5.2. Lennox-Gastaut Syndrome

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 2 AEDs (including VNS), and have had at least 4 documented convulsive seizures 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. 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 1 subject.

No clinical signs of valvular heart disease (VHD) or pulmonary arterial hypertension (PAH) have been observed in any patients in the Belgian cohort (ZX008 IB 2022v.10.0).

1.6. Rationale for Current Study

As described above, Zogenix has conducted 2 positive double-blind, randomized, placebo-controlled studies in Dravet syndrome. Additionally, long-term safety and efficacy data for up to 3 years in some subjects has been collected. Based on the results from Study 1 and Study 1504 in Dravet syndrome, Zogenix has submitted a New Drug Application (NDA) to the United States Food and Drug Administration, and a Marketing Authorization Application (MAA) to the European Medicines Agency. Zogenix also has one double-blind placebo-controlled study ongoing in Lennox-Gastaut syndrome (Study 1601; NCT number:

NCT03355209). This is a 2-part study. Part 1 is a double-blind, parallel-group, placebo-controlled study to assess the efficacy and safety of 2 doses of ZX008 when used as adjunctive therapy for seizures in children and adult subjects with LGS. The primary study endpoint is assessed from Part 1 data. Part 2 is a 1-year open-label, flexible-dose extension for subjects completing Part 1 of the study.

Study 1503 is soon to be completed, and Study 1601 Part 2 provided treatment for up to 1 year. The main purpose of this open-label study is to continue to provide treatment to patients with Dravet syndrome or Lennox-Gastaut syndrome who may still derive clinically meaningful benefit from ZX008 after completing Study 1503 or Study 1601 Part 2, until the product is

approved, or a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first.

This study (1) additionally provides an opportunity to continue to evaluate the long-term safety of ZX008 in Dravet syndrome and Lennox-Gastaut syndrome until the product is approved and available via prescription; and, (2) may serve as an open-label extension study for patients with rare seizure disorders and epileptic encephalopathies who have participated in other Zogenix-sponsored clinical trials of ZX008.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objective of the study is to assess the long-term safety and tolerability of ZX008.

2.2. Secondary Objectives

- To assess the effect of ZX008 on the following effectiveness measures:
  - Investigator assessment of convulsive seizure response (<25%, ≥25%, ≥50%, ≥75%, or 100% [ie, seizure-free] improvement)
  - Clinical Global Impression – Improvement (CGI-I) rating, global and symptomatic, as assessed by the investigator
  - CGI-I rating, global and symptomatic, as assessed by the parent/caregiver

2.3. Study Endpoints

2.3.1. Safety Endpoints

The safety endpoints of the study are:

- AEs
- Laboratory safety (hematology, chemistry)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Physical examination
- Neurological examination
- Electrocardiogram (ECGs)
- Doppler echocardiogram (ECHOs)
- Body weight/height
- Chest x-ray (subjects in France and Netherlands only)
- Electroencephalogram (EEG) (in Italy only)

Laboratory safety parameters (hematology, chemistry), ECGs, EEGs (in Italy only), and chest-x-ray (in France and Netherlands only), will only be assessed as clinically indicated.

For results disclosure on public registries (e.g ClinicalTrials.gov and EudraCT), only incidence of TEAEs will be publicly disclosed as a Primary Endpoint. The remaining Safety Endpoints are considered as other for the purpose of public data disclosure.

2.3.2. Effectiveness Endpoints

The effectiveness endpoints of the study are:

- CGI-I, global and symptomatic, as assessed by parent/caregiver
- CGI-I, global and symptomatic, as assessed by investigator (or designee)
- Percent improvement in seizure burden as assessed by the investigator (or designee)

Assessments by the investigator (or designee) should be performed by the same rater for each subject whenever possible. If the rater changes permanently, a new baseline CGI-S (Appendix 3) should be established (see Section 7.1).

The same parent/caregiver should perform each assessment. If the same parent/caregiver is not available, the assessment should be skipped.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is an international, multicenter, open-label, long-term safety study of ZX008 in patients with epileptic encephalopathy, including Dravet syndrome or Lennox-Gastaut syndrome. Subjects eligible for participation are those with Dravet syndrome who are currently enrolled in Study ZX008-1503, or those with Lennox-Gastaut syndrome who have successfully completed Study ZX008-1601-Part 2, and are candidates for continued treatment with ZX008 for an extended period of time, or those with Dravet syndrome, Lennox-Gastaut syndrome, or another epileptic encephalopathy who have completed participation in another Zogenix-sponsored study and have been invited to participate in this study.

Subjects having transitioned from ZX008-1503, ZX008-1601 or who have participated in another Zogenix-sponsored study will be eligible to participate in this trial until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first.

All subjects who discontinue from the study treatment and do not transition directly to commercial product will undergo up to 2-weeks taper of study medication. (Note subjects enrolled in the United Kingdom will have an additional follow-up safety visit 12 months after the last dose; subjects enrolled in Germany, France, and Netherlands will have an additional follow-up safety visit at 24 months after the last dose).

Subjects entering this OLE study who have participated in 1503 or 1601 will receive ZX008 initially at the dose prescribed at the last visit in Study 1503 or Study 1601 Part 2, but will have the volume adjusted according to weight of the patient. Dose increases, to a maximum of 0.8 mg/kg/day (maximum 30 mg/day) for subjects not receiving concomitant STP or 0.5 mg/kg/day (maximum 20 mg/day) for subjects receiving concomitant STP, during this OLE study should not occur more frequently than every 7 days in dose increments of not more than 0.2 mg/kg/day. Dose increases (as per mg/kg) may only occur after a review of reported adverse events (AEs), and if, in the investigator's opinion, seizure frequency, severity, or duration indicates a change in medication regimen is warranted. Dose decreases for tolerability or safety concerns can occur at the investigator's discretion, in dose amounts and frequency appropriate for the clinical situation. ZX008 dose adjustments outside of these parameters should be discussed with the CRO Medical Monitor prior to initiation.

Changes in dosage of concomitant AEDs may be implemented as clinically necessary, and concomitant AEDs may be withdrawn completely, but all subjects must remain on a minimum of 1 concomitant AED plus ZX008 unless it is deemed clinically appropriate by the investigator (after discussion with the CRO Medical Monitor) to dose as monotherapy. New concomitant AEDs or anti-epileptic treatments may be introduced at the investigator's discretion, as would be typically indicated in clinical practice. Clinical worsening leading to a change in medication must be documented in the source notes and case report form (CRF) and all medication dose

changes must be documented with a clinical explanation and justification. Any addition of a new AED must be discussed with the CRO Medical Monitor prior to implementation.

Echocardiograms (ECHO) and other safety assessments detailed in the schedule of assessments (SoA) will be conducted every 6 monthsunless more frequent follow-up is clinically indicated or required by the Sponsor or IDSMC. A follow-up visit and a cardiac safety assessment will be performed after study drug discontinuation for subjects who do not transition to commercially available ZX008. Subjects who transition to commercially available ZX008 will not return for a follow-up after EOS/ET or a cardiac follow up after last dose but must have had an ECHO within 3 to 6 months before the transition date and will have follow-up ECHOs within required timeframe while on commercial drug supply.

Caregivers will be asked to use a diary to record the number/type of seizures to support investigator determination of treatment benefit; however, diary data collection is not mandatory, nor will it be collected in the database. A schedule of assessments is provided in Table 1.

3.2. Number of Subjects

Up to approximately 650 subjects from the core studies may be enrolled. The number of subjects is dependent on the number who participate in Study ZX008-1503 or ZX008-1601 Part 2 and who volunteer for the extension study and meet the necessary criteria for enrollment.

3.3. Study Duration

Subjects having transitioned from ZX008-1503, ZX008-1601 or who have participated in another Zogenix-sponsored study, will be eligible to participate in this trial until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first..

All subjects who discontinue from the study treatment and do not transition directly to commercial product will undergo up to 2-weeks taper of study medication. (Note subjects enrolled in the United Kingdom will have an additional follow-up safety visit 12 months after the last dose; subjects enrolled in Germany, France, and Netherlands will have an additional follow-up safety visit at 24 months after the last dose).

3.4. Number of Study Centers

The study expects approximately 150 participating research centers in North America, Europe, Australia, and Japan.

3.5. Rationale for Study Design

All subjects enrolled will receive ZX008. Dose administration is intended to be consistent with that of intended clinical practice. The duration of the studywill allow for collection of appropriate data to further characterize the safety profile of ZX008.

3.6. Premature Termination of Study

The Sponsor can terminate the study prematurely at any time for medical, ethical, or business reasons at individual study sites or at all study sites. The investigator will be notified in writing and instructions will be provided for termination procedures.

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 alternative therapy is available and that End-of-Study procedures are conducted, as described in Section 6.1.3 and Section 6.2.

All study materials including investigational medicinal product (IMP) 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)/Institutional Review Board (IRB).

3.7. Study Monitoring Procedures

3.7.1. Independent Data and Safety Monitoring Committee (IDSMC)

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

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

The IDMSC will:

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

The responsibilities of the IDSMC on the safety oversight can be transferred back to the Sponsor at any time during the course of the study.

3.7.2. 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, 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.

4.1. Inclusion Criteria

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

1. Subject is currently enrolled in core Study ZX008-1503 and remains a candidate for continuous treatment for an extended period of time.

   OR

   Subject has successfully completed core Study ZX008-1601-Part 2 and remains a candidate for continuous treatment for an extended period of time.

   OR

   Subject with epileptic encephalopathy has successfully completed another Zogenix-sponsored clinical trial with ZX008, remains a candidate for continuous treatment for an extended period of time, and has been invited to participate in this study by the Sponsor.

2. Subjects must, in the medical opinion of the Investigator, be candidates for continued treatment for an extended period of time with ZX008 (ie, subject has demonstrated a clinically meaningful benefit with ZX008 in the prior trial, and benefits of continued treatment outweigh potential risks).
3. Subject is male, or nonpregnant, nonlactating female. Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative pregnancy test prior to study entry. Subjects of childbearing or child-fathering potential must be willing to use medically acceptable forms of birth control, which includes abstinence, while being treated on this study and for 90 days after the last dose of study drug.
4. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
5. Subject has provided assent in accordance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements, if capable.
6. Subject's caregiver is willing and able to be compliant with study procedures, visit schedule and study drug accountability.

4.2. Exclusion Criteria

Subjects meeting 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 has current cardiac valvulopathy or pulmonary hypertension that the investigator, ICAB, IDSMC, or Sponsor deems reason for exclusion

3. 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 as measured by the CSSRS Since Last Visit, 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.
4. Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x upper limit of normal [ULN] and/or elevated bilirubin < 2x ULN) may be entered into the study after review and approval by the CRO Medical Monitor in conjunction with the Sponsor, in consideration of comorbidities and concomitant medications.
5. Administration of a prohibited medication (see section 5.6.2), within 14 days of receiving ZX008.
6. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
7. Subject has a clinically significant condition, or has had clinically relevant symptoms or a clinically significant illness at Visit 1, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject, including chronic obstructive pulmonary disease, interstitial lung disease, or portal hypertension.
8. Subject has participated in another clinical treatment trial within the past 30 days (ie, the last visit of the previous study was in the past 30 days), with the exception of a ZX008 clinical study.

4.3. 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, must comply with the contraceptive requirements detailed above.

4.3.1. 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.

4.3.2. 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 subject 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 and should complete the taper schedule.

4.4. 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 CRF. 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:

1. Development of signs or symptoms indicative of cardiac valvulopathy or regurgitation (mitral, aortic, tricuspid, pulmonary valves), or pulmonary hypertension for which IDSMC or the Sponsor, in consultation with the ICAB, the central cardiac reader, 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 and continued participation puts the subject and/or outcomes of the study at risk.
3. Subject requires or starts using an unacceptable or prohibited concomitant medication.
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. In the opinion of the investigator or Sponsor, 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. Subject experiences clinically significant worsening of seizures or other symptoms for which the investigator determines treatment with ZX008 is no longer beneficial. 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.
8. Subject experiences significant weight loss as determined by the investigator, that has not stabilized or recovered.
9. An "actual suicide attempt" as classified by the C-SSRS.

10. It is the investigator's or Sponsor's opinion that it is not in the subject's best interest to continue in the study.
11. 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. Discontinuation decisions due to development of cardiovascular or cardiopulmonary complications may be made by the IDMSC or the Sponsor, with input from the ICAB and the investigator.

If feasible, the process of discontinuation should be discussed with the CRO 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 CRO Medical Monitor, but final decisions about the process will remain at the discretion of the site principal investigator.

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, etc)

The IDSMC may request that the study be terminated after review of the safety information at any time during the study.

In the event that the study is terminated prematurely then the procedure for termination should be followed as described in Section 3.6.

The reason for, and date of discontinuation from participation in the study must be recorded in detail in the CRF 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 are described in Section 6.1.3 and Section 6.2. 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.

4.5. Termination of the Clinical Study

If the investigator, the Sponsor, the CRO 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

4.6. Replacement of Subjects

Enrolled subjects will not be replaced.

5. INVESTIGATIONAL MEDICINAL PRODUCT INFORMATION

ZX008 will be administered in the current study. A brief description of the ZX008 product is provided below (Table 2).

Table 2. 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 2.5 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 a concentration of 2.5 mg/mL. The excipients selected have been approved for use in the formulations of currently marketed drug products and are considered to be [redacted] The solution formulation 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 ketogenic diet (KD). The formulation will be provided in bottles with tamper-evident, child-resistant caps.

Flexible dosing will be studied, up to 0.8 mg/kg/day divided into 2 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). 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 fulfil the dose. **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.

5.1.1. Labeling and Packaging

The ZX008 product will be packaged and labeled according to current ICH, Good Manufacturing Practices (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.

5.2. 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. The 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.

5.3. Investigational Medicinal Product 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 bottles to the subject will be handled through an 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, 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.

5.4. Treatment Administration

5.4.1. Open-label Extension Treatment Period

The investigator (or delegate) will dispense IMP only to subjects included in 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, with or without food. Each dose should be separated by a

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

During the OLE Treatment Period, all subjects will continue receiving ZX008 at the dose prescribed at the last visit in Study 1503 or Study 1601 Part 2 but will have the volume adjusted according to weight of the patient. The starting dose for subjects entering this study from another Zogenix-sponsored clinical study of ZX008 (not to exceed 0.8 mg/kg/day or 30 mg/day) will be determined through consultation between the investigator and CRO Medical Monitor. Dose increases, to a maximum of 0.8 mg/kg/day (maximum 30 mg/day) for subjects not receiving concomitant STP or 0.5 mg/kg/day (maximum 20 mg/day) for subjects receiving concomitant STP, during this OLE should not occur more frequently than every 7 days in dose increments of 0.2 mg/kg/day.

Dose changes should be made in increments of 0.2 mg/kg/day, as follows:

- Subjects who are not receiving concomitant STP: may increase to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day
- Subjects who are receiving concomitant STP: the first dose change will be to 0.4 mg/kg/day and the final dose change will be to 0.5 mg/kg/day, but not to exceed 20 mg/day

Dose increases (as per mg/kg) may only occur after a review of seizures and reported AEs, and if, in the investigator's opinion, seizure frequency, severity, and/or duration indicates a change in medication regimen is warranted. Dose decreases for tolerability can occur at the investigator's discretion, in dose amounts and frequency appropriate for the clinical situation. ZX008 dose adjustments outside of these parameters should be discussed with the CRO Medical Monitor prior to initiation.

Changes in dosage of concomitant AEDs may be implemented as clinically necessary, and concomitant AEDs may be withdrawn completely, but all subjects must remain on a minimum of 1 concomitant AED plus ZX008 unless it is deemed clinically appropriate by the investigator (after discussion with the CRO Medical Monitor) to dose as monotherapy. New concomitant AEDs or anti-epileptic treatments may be introduced at the investigator's discretion, as would be typically indicated in clinical practice. The description of clinical worsening must be documented in the source notes and case report form (CRF) and all medication dose changes must be documented with a clinical explanation and justification. Any addition of a new AED must be discussed with the CRO Medical Monitor prior to implementation.

5.4.2. Taper Period

All subjects (those who complete the 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 3.

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 3. Taper Algorithm

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).

5.5. Blinding

This is an open-label study.

5.6. Prior and Concomitant Medication

All medications taken by a subject after the first administration of IMP in this study, and 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 1 concomitant AED during study participation. Changes in dosage of concomitant AEDs may be implemented as clinically necessary, and concomitant AEDs may be withdrawn completely, but all subjects must remain on a minimum of 1 concomitant AED plus ZX008. New concomitant AEDs or anti-epileptic treatments may be introduced at the investigator's discretion, if there is a clinically meaningful worsening in seizure type, frequency, and/or duration. A clinically meaningful worsening would be an increase in frequency, severity or duration of existing seizures, or emergence of a new seizure type that is not associated with a transient illness. The description of clinical worsening must be documented in the source notes and case report form (CRF) and all medication dose changes must be documented with a clinical explanation and justification. Any addition of a new AED must be discussed with the CRO Medical Monitor.

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.

5.6.1. 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.

5.6.2. Prohibited and Restricted Concomitant Medications

The following concomitant medications/foods are prohibited during the clinical trial:

- Alcohol in all forms (wine, beer, liquors) and amounts is prohibited during the study.
- Felbamate is prohibited as a concomitant medication unless the subject has been on felbamate for at least 18 months prior to the core study Screening visit, has stable liver function and hematology laboratory tests, and the dose is expected to remain constant throughout the study.
- Drugs that increase cardiovascular risk: e.g., atomoxetine
- Drugs intended to facilitate weight loss and centrally-acting anorectic agents: e.g. Lorcaserin, Phentermine, Naltrexone-bupropion, Phentermine-topiramate, Diethylpropion, Benzphetamine-Phendimetrazine
- Monoamine oxidase inhibitors (MAOIs): e.g. Isocarboxazid, Selegiline, Tranylcypromine, Phenelzine

Chronic/long term use of a prohibited medication is considered a major protocol deviation

Restricted Concomitant Medication
A representative list of medications that should be avoided, if possible, during study participation is provided in Appendix 1. If medical necessity requires the use of 1 or more medications listed in Appendix 1 during the course of the study, the CRO Medical Monitor must first be contacted for approval.

The list includes, but is not limited to:

- Drugs that interact with central serotonin should be avoided: e.g., selective serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements such as St. John's Wort and tryptophan, drugs that impair metabolism of serotonin, dextromethorphan, lithium, tramadol, and antipsychotics with serotonergic agonist activity. Subjects receiving these medications should be monitored closely for the emergence of signs and symptoms of Serotonin syndrome, which include mental status changes (e.g. agitation, hallucinations and coma) autonomic instability (e.g. tachycardia, labile blood pressure and hyperthermia), neuromuscular aberrations (e.g. hyperreflexia and incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting and diarrhea). If serotonin syndrome is suspected, treatment with ZX008 should be stopped immediately and symptomatic treatment should be started.Cyproheptadine is a potent serotonin receptor antagonist and may therefore decrease the efficacy of ZX008. If cyproheptadine is used in conjunction with ZX008, patients should be monitored appropriately.

- Chloroquine or Hydroxychloroquine is prohibited during the study unless prescribed in urgent cases for short term use with approval from the CRO Medical Monitor.

5.7. Treatment Compliance

Subjects will bring their used, partially used, and unused IMP to every study visit. Treatment compliance will be monitored by measuring the volume by weight of IMP in these bottles and comparing to the dispensation log.

6. VISIT SCHEDULE

Study procedures will be conducted according to the Schedule of Assessments in Table 1. Time windows for all assessments are detailed in Table 4.

Table 4. Time Windows for Assessments

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Clinic; Study Day 1)	Not applicable: same as the last visit in Study 1503 or Study 1601 Part 2, or other ZX008 study as applicable
Visits 2, 3, 4, 5, 6 (Months 6, 12, 18, 24, 30; Days 180, 360, 540, 720, 900)	± 7 days
Visit 7 (EOS; Study Day 1080) [a] Visit 8 (EOS/ET + 14 days)	
Visit 9 (Last Dose + 6 months)[b]	± 7 days

[a] Subjects will receive ZX008 treatment in this study until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subject's country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first. In that regard, participation could be extended beyond 36 months if none of the conditions above mentioned are met.

[b] Depending on country requirements. See Table 7 for details.

6.1. Open-label Extension Treatment Period

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 this study must be obtained before a subject can start any of the Visit 1 procedures. For subjects entering this OLE study from Study 1503 or Study 1601 Part 2, Visit 1 will be the same as the last visit in Study 1503 or Study 1601 Part 2. Assessments conducted at the End of Study Visit of 1503 or 1601 Part 2 that are identical to assessments required at Visit 1 will not be repeated. Continuation of treatment in this study should be discussed at the start of the visit. For subjects who wish to continue, informed consent/assent must be obtained before conducting any assessments or distributing study drug under this protocol. Visit 1 will be identical to the last visit of another ZX008 study, as applicable, and the same rules will apply for assessments and continuation.

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.

Only eligible subjects as specified by the inclusion and exclusion criteria who have successfully completed the core study and who meet all other eligibility criteria will be enrolled into study ZX008-1900.

6.1.1. Clinic Visit 1 (Study Day 1; Transition Visit)

Assessments conducted at the End of Study Visit that are identical to the assessments listed below will not be repeated. However, data associated with these assessments will be entered in the eCRFs.

- Obtain written informed consent for the study
- Review inclusion and exclusion criteria
- Record demographic information
- Record medical epilepsy history
- Record concomitant medications
- Complete abbreviated physical examination, as clinically indicated based on medical history, and/or signs/symptoms. Abnormal clinically significant findings must be reported as adverse events.
- Record height, weight, and calculation of BMI
- Complete abbreviated neurological examination, as clinically indicated based on medical history, and/or signs/symptoms. Abnormal clinically significant findings must be reported as adverse events.
- ECG, as clinically indicated (conducted and read locally). Abnormal clinically significant findings must be reported as adverse events.
- Doppler ECHO
- Chest X-ray (in France and Netherlands only), as clinically indicated. Abnormal clinically significant findings must be reported as adverse events.
- EEG (in Italy only), as clinically indicated. Abnormal clinically significant findings must be reported as adverse events.
- Vital signs
- Pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, hematology)
- C-SSRS Since Last Visit Assessment (Appendix 2)
- CGI-Severity (assessed by parent/caregiver)
- CGI-Severity (assessed by investigator)
- Seizure assessment (assessed by investigator)
- Record AEs
- Dispense study medication

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.

6.1.2. Clinic Visits 2, 3, 4, 5, 6 (Months 6, 12, 18, 24, 30)

Subjects will report to the clinic in the morning of Clinic Visits 2 through up to Visit 6. The following procedures will be performed:

- Record concomitant medications
- Abbreviated physical examination, as clinically indicated. A full physical and/or neurological examination may be performed, if warranted. Abnormal clinically significant findings must be reported as adverse events.
- Abbreviated neurological examination, as clinically indicated. A full physical and/or neurological examination may be performed, if warranted. Abnormal clinically significant findings must be reported as adverse events.
- Height and weight, and calculation of BMI
- Obtain vital signs
- ECG, as clinically indicated (conducted and read locally). Abnormal clinically significant findings must be reported as adverse events.
- Doppler ECHO
- Chest X-ray (in France and Netherlands only), if clinically indicated, Abnormal clinically significant findings must be reported as adverse events.
- EEG (in Italy only), if clinically indicated, Abnormal clinically significant findings must be reported as adverse events.
- Pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry and hematology), as clinically indicated. Abnormal clinically significant findings must be reported as adverse events.
- Collect plasma sample for AED PK evaluation (as clinically indicated)
- C-SSRS Since Last Visit Assessment (Appendix 2)
- CGI-I, global and symptomatic (assessed by parent/caregiver)
- CGI-I, global and symptomatic (assessed by investigator)
- Seizure assessment (assessed by investigator)
- Record AEs
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.1.3. Clinic Visit 7 (Month 36): End of Study/Early Termination

The End-of-Study participation for an individual subject occurs when approval of ZX008 has been obtained from regulatory authorities for the subject's indication, when a managed access program is established as allowed per country-specific requirements in addition to legal and

regulatory guidelines in the subjects country of residence, or when the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first. In that regard, participation could be extended beyond 36 months if none of the conditions above mentioned are met at Visit 7.

. The End-of-Study visit may also occur if the subject withdraws participation from the study.

Subjects will visit the clinic for the End-of-Study Visit if 1 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.
4. ZX008 is approved by regulatory authorities for the subject's indication, a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first.

The following procedures will be performed:

- Record concomitant medications
- Abbreviated physical examination, as clinically indicated. A full physical and/or neurological examination may be performed, if warranted. Abnormal clinically significant findings must be reported as adverse events.
- Abbreviated neurological examination, as clinically indicated. A full physical and/or neurological examination may be performed, if warranted. Abnormal clinically significant findings must be reported as adverse events.
- Height and weight, and calculation of BMI
- Obtain vital signs
- ECG, as clinically indicated (conducted and read locally). Abnormal clinically significant findings must be reported as adverse events.
- Doppler ECHO
- Chest X-ray (in France and Netherlands only), as clinically indicated, Abnormal clinically significant findings must be reported as adverse events.
- EEG (in Italy only), as clinically indicated, Abnormal clinically significant findings must be reported as adverse events.
- Pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry and hematology), as clinically indicated. Abnormal clinically significant findings must be reported as adverse events.
- Collect plasma sample for AED PK evaluation (as clinically indicated)
- C-SSRS Since Last Visit Assessment (Appendix 2)

- CGI-I, global and symptomatic (assessed by parent/caregiver)
- CGI-I, global and symptomatic (assessed by investigator)
- Seizure assessment (assessed by investigator)
- Record AEs
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

6.2. EOS/ET Follow Up Visit (Clinic Visit 8; EOS/ET +14 days)

If the subject completes the study (or discontinues from the study early), and is not switching to commercially available drug, the subject will visit the clinic 14 days after the EOS/ET). The following procedures will be performed at the 14 day follow up visit:

- Abbreviated physical examination (as appropriate based on last exam and reported AEs)
- Abbreviated neurological examination (as appropriate based on last exam and reported AEs).
- Record AEs
- Record Concomitant Medications
- Weight
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver

6.3. Cardiac Follow Up Visit (Clinic Visit 9; last dose + 6 Months)

If the subject completes the study (or discontinues from the study early), and is not switching to commercially available drug, the subject will visit the clinic 6 months after the last dose. At the 6 month follow up visit, the following procedures will be performed, with additional follow-ups based on country of residence (see table 5).

- Abbreviated physical/neurological examination. A full physical and/or neurological examination may be performed, if warranted. Abnormal clinically significant findings must be reported as adverse events.
- 12-lead ECG (conducted and read locally)
- Doppler ECHO
- Record AEs
- Record concomitant medications

If the subject completes the study or discontinues from the study early, the subject will return to the clinic for follow-up cardiac testing (ECHO, ECG, and in some cases, physical examination). The timing and frequency of exams are in Table 5. 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 ECHO, ECG and/or physical examination should continue to be followed until the finding is resolved or stable and unlikely to change, with reports submitted as AEs to the ZX008 safety database.

If the subject completes the study (or discontinues from the study early) and is switching to commercially available drug, the subject will complete the EOS visit and follow the drug administration process outlined for commercial product as advised by the subject's physician. The EOS/ET and cardiac follow-up visits are not required.

Table 5. Schedule of Post-Treatment Cardiac Follow-up

Parameter		Have had any clinically significant cardiac sign or symptom regardless of the time on study drug[a]
ECHO and ECG	Follow-up 6 months post-treatment[b] in UK: additional 12-month follow-up in Germany, France, Netherlands: additional 24-month follow-up	Follow-up 6-24 months post-treatment[b], and every 6 months until resolved, or stable and unlikely to change
Physical examination	Follow-up 14 days after EOS ET and 6 months post- treatment only	Follow-up 6 months post- treatment, and every 6 months until resolved, or stable and unlikely to change
Chest x-ray (subjects enrolled in France or Netherlands only)	Follow-up 6, and 24 months post-treatment	Follow-up 6, and 24 months post- treatment and every 6 months until resolved, or stable and unlikely to change

[a] 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] Subjects who discontinue and do not continue with commercially available drug are required to have follow-ups at 6 months post-treatment. Subjects enrolled in the UK will also have an additional 12-month follow-up. Subjects enrolled in Germany, France, and Netherlands will have an additional 24-month follow-up.

6.4. Estimated Blood Volume Collection

The maximum total blood volume collected during the study for clinical laboratory testing and PK will be approximately 80.5 mL, as outlined in Table 6.

Table 6. Estimated Blood Volume Collection[a]

Assessment/ (Study Day)	OLE Treatment Period (Study Day)			
	1	180, 360, 540, 720, 900	1080[b]	Total
Clinical chemistry	7.5	7.5 mL at each visit	7.5 mL	52.5 mL
Hematology	2	2 mL at each visit	2 mL	14 mL

Assessment/ (Study Day)	OLE Treatment Period (Study Day)			
	1	180, 360, 540, 720, 900	1080[b]	Total
AED plasma sample	1 x 2 mL	1 x 2 mL at each visit	1 x 2 mL	14 mL
Approximate total blood volume per subject	11.5 mL	11.5 mL at each visit	11.5 mL	**80.5 mL**

[a] In concordance with The Seattle Children's Research Foundation Guidance (Appendix 3), blood collection volumes for children weighing up to 15 kg will be:

- the maximum allowable volume of blood in 1 draw is 22-30 mL (2.5% of total blood volume)
- the maximum in a 30-day period is 44-60 mL

[b] If the participation of the subject is extended beyond day 1080, 11.5 mL of blood will be collected per extra visit.

6.5. Specific guidance related to COVID-19 pandemic

In alignment with health authority regulations, such as the US Food and Drug Administration and European Medicine Agency, protocol exceptions may be made where necessary to eliminate apparent immediate hazards to study patients.

Subjects may not be able to attend their next visit because they cannot/will not travel or they are not allowed to visit the hospital except for emergency cases. Principal Investigators and study site personnel are asked to work closely with their patients to determine a course of action that supports the rights, safety and welfare of participants and ensure as little impact on the integrity of the research as possible.

Should any study visit be impacted by the COVID-19 pandemic (e.g. shelter in place, travel restrictions, etc...) please refer to appendix 6 for further guidance on visit scheduling, occurrence, and assessment completion.

7. EFFECTIVENESS, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

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

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

7.1. Effectiveness Assessments

For all ratings, the same evaluator (at the clinical site and parent/caregiver) will 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 ratings completed by the parent/caregiver, if the same parent/caregiver cannot complete the rating at a visit, the rating will not be completed.

7.1.1. Seizure Assessments

Based on discussions with the parent/caregiver, clinical evaluation, and review of an optional seizure diary, the percent improvement in seizure burden will be assessed by the investigator on a 5-point scale: <25%, ≥25%, ≥50%, ≥75%, 100% [ie, seizure-fee] improvement.

7.1.2. Clinical Global Impression - Severity

At Visit 1 of this OLE study, both the parent/caregiver and the investigator will rate their global impression of the subject's condition in order to establish a reference baseline for ongoing CGI-I ratings.

The investigator and the parent/caregiver (independently) will perform 4 ratings (Appendix 3). The severity of a patient's condition overall, and for each of the 3 symptoms of interest (cognition, behavior, and motor abilities) will be rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) as follows:

1=normal, not at all ill
2=borderline ill
3=mildly ill
4=moderately ill
5=markedly ill
6=severely ill
7=among the most extremely ill

The parent/caregiver will be asked to indicate the appropriate response that adequately describes the subject's condition overall and symptoms relative to expectations for age and development.

The investigator will be asked to indicate the appropriate response that adequately describes how the subject's condition overall and symptoms relative to their total clinical experience with this patient population.

7.1.3. 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.

The Clinical Global Impression (CGI) scale measures the change in the subject's clinical status from a specific point in time. The CGI rating scale permits a global evaluation of the subject's improvement over time.

The investigator and the parent/caregiver (independently) will perform 4 ratings (Appendix 4). The improvement of a patient's condition overall, and for each of the 3 symptoms of interest (cognition, behavior, and motor abilities). The improvement 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 the subject's overall condition has improved or worsened relative to the rating provided at Visit 1.

The investigator will be asked to indicate the appropriate response that adequately describes how the subject's overall condition has improved or worsened relative the rating provided at Visit 1.

7.2. Safety Assessments

7.2.1. Demographics, Epilepsy History, and Concomitant Medication

Subject demographics, diagnosis (ie, Dravet syndrome or Lennox-Gastaut syndrome), and current medications will be carried over from the core study.

7.2.2. Physical Examinations

Abbreviated physical examinations will be conducted by the investigator or designee during the study as outlined in Table 1. An abbreviated physical examination will be based on medical history and/or signs/symptoms and cover the following body systems: heart, lungs, and follow up of other systems as appropriate based on last exam and reported AEs. A full physical examination (ie, general appearance, skin, eyes, ears, nose, throat, heart, lungs, abdomen, neurological system, lymph nodes, spine, and extremities) may be performed, if warranted. Abnormal clinically significant observations must be reported as adverse events.

7.2.3. Neurological Examinations

Abbreviated neurological examinations will be conducted by the investigator or designee during the study as outlined in Table 1. 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. A full neurological examination (ie, cranial nerves, muscle strength and tone, reflexes, coordination, sensory function, and gait) may be performed, if warranted. Abnormal clinically significant observations must be reported as adverse events.

7.2.4. Vital Signs

Vital signs including blood pressure, heart rate, temperature, and respiratory rate will be documented for subjects during study as outlined in Table 1.

7.2.5. Laboratory Measurements

Laboratory safety parameters will be analyzed as clinically indicated, using standard validated methods. Parameters to be assessed will be at the discretion of the investigator.

The following parameters may be assessed by the laboratory as described in Table 1:

- Hematology: hemoglobin, hematocrit, erythrocytes, erythrocyte mean corpuscular volume, leukocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets
- Blood Biochemistry: albumin (ALB), alkaline phosphatase (AP), alanine aminotransferase (ALT; SGPT), aspartate aminotransferase (AST; SGOT), bicarbonate, blood urea nitrogen (BUN), calcium (Ca), chloride (Cl), creatinine, creatine kinase, gamma-glutamyl transferase (GGT), globulin, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid.
- Urine or serum pregnancy test: Pregnancy testing will be performed in female subjects of childbearing potential.

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, the investigator must sign and date the laboratory report.

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.

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 will be documented in the CRF as an AE (Section 9).

7.2.6. 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 when clinically indicated, as outlined in Table 1.

7.2.7. Electrocardiograms

Twelve-lead ECGs will be conducted as clinically indicated 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.

7.2.8. Doppler Echocardiography

Doppler echocardiography will be conducted at a facility with experience for the subject's age during study as outlined in Table 1. 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. A manual of proper ECHO technique for sites is provided in a separate document.

7.2.9. 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 clinically indicated.

7.2.10. Electroencephalogram (EEG) (Italy only)

Routine electroencephalogram (r-EEG) will be obtained as clinically indicated 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.

7.2.11. Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (Appendix 2) will be assessed during study as outlined in Table 1. 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. The C-SSRS version 1/14/19 (Since Last Visit) will be used in this study as appropriate for the age and level of intellectual development.

Subjects who are younger than 7 years chronologically, or who are judged by the investigator not to have the mental capacity to understand the questions as specified on the C-SSRS, will not complete the rating. The investigator should use his/her judgment to substitute intellectually-appropriate questions to probe the tendency for self-harm.

If a subject with the intellectual capacity to complete the C-SSRS has their 7th birthday during the study, use of the C-SSRS should be initiated at subsequent visits.

7.2.12. Adverse Events

Adverse events 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. For subjects who participated in 1 of the core studies, adverse events that occur after signing informed consent for this study, but before Visit 1 will be recorded as adverse events in the core study and medical history in ZX008-1900.

Details of the definitions and categorization of AEs, and procedures for the reporting of AEs, are available in Section 8.

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. All AEs will be recorded on the appropriate CRF page.

7.3. 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 Visit 1 of ZX008-1900 until the end of study. Adverse events that occur after signing informed consent for this study, but before Visit 1 will be recorded as adverse events in the core study and medical history in ZX008-1900.

Adverse events may include:

- Illness present before core study entry should be recorded in the medical history section of the CRF along with any ongoing AEs that were present at the last visit of the core study. These events should only be reported as an AE if there is an increase in the frequency or severity of the condition from the core study
- Exacerbation of seizures is considered an AE if there was an increase in frequency beyond the subject's typical pre-core study fluctuations, or in the event that seizures lengthen in duration in a clinically meaningful way compared with core study 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 CRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the CRF 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 1 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). A single episode of SE in a 24-hour period, regardless of whether rescue medication was administered, should be entered in the AE log. If 2 or more episodes occur within 24 hours, each lasting 30 minutes or more, an SAE of SE should be recorded. Hospitalization to manage SE, regardless of the number of episodes, should be reported as an SAE.

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

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 7).

Table 7. Severity Definition of Adverse Events[a]

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.

[a] Clinical Data Interchange Standards Consortium Study Data Tabulation Model Severity Intensity Scale for Adverse Event Terminology

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:

1. Not Related: Concomitant illness, accident or event with no reasonable association with study drug.
2. 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 will start at Visit 1 of ZX008-1900 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 study from 1 of the core studies, ongoing AEs from the core studies will be considered medical history unless there is an increase in the frequency or severity of the condition from the core 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 CRF. 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 CRF.

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

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:

All SAEs that occur during the course of the study, beginning at Visit 1, whether or not causally related to IMP must be reported immediately via telephone or email or EDC (within 24 hours of the investigator becoming aware of the event) to the Sponsor or the CRO Medical Monitor.

1. Enter all relevant information into SAE eCRF, via the EDC.
2. In the event that EDC is down or not accessable the site can send a paper SAE form to the Safety team within 24 hours of becoming aware of the SAE and then enter the SAE into the eCRF page once the EDC is back up and accessible.

Adverse events occurring in the period between the time the subject gave written informed consent and the first exposure to IMP that meet 1 or more of the seriousness criteria for AEs must be reported to the Sponsor and the CRO 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 and the CRO Medical Monitor**.

Contact details and guidance for reporting SAEs are provided below:

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com

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 and the CRO 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 CRF.

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.

When submitting SAE reports to the Sponsor, 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 any time that additional relevant information becomes available. In cases of death, the investigator should supply the Sponsor 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'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. For results disclosure on public registries (e.g ClinicalTrials.gov), treatment-emergent serious adverse events will be included.

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 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 CRO 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's Global Clinical Safety and Pharmacovigilance and the CRO 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.

8.9.1. Follow-up of Echocardiogram Findings

All ECHOs will be evaluated by a central reader from ERT, Inc. (ERT), in consultation with the ICAB, if warranted. Findings related to pulmonary hypertension or valvulopathy on any of the 4 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 1-3. Table 8 describes the severity of ECHO findings with the level of increasing oversight if the subject is to remain in the study.

Table 8. 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 1	Level 1	Level 1
Mild (>18 years)	Level 2	Level 1	Level 1	Level 1
Moderate	Level 3	Level 2	Level 2	Level 2
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 if available 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, VPA, CLB, 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 risk 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 or Sponsor safety representative/physician for review, including consideration of effects on seizures and comorbidities.
4. The Co-Chairs of the ICAB are alerted to the request and prepare, after consultation with an evaluation of the cardiopulmonary risk and proposed monitoring plan if applicable, for submission to the IDSMC or Sponsor safety representative/physician.
5. IDSMC/Sponsor safety representative/physician will review the submission from the Investigator and the ICAB.
6. IDSMC/Sponsor safety representative/physician 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 if available and consult with the parent/guardian, and determine whether the achieved benefit justifies the consideration of continuing study treatment by the IDSMC/Sponsor safety representative/physician. Minimal efficacy criteria for IDSMC/Sponsor safety representative/physician consideration:
   a. Seizures must be more than 75% improved (number of convulsive 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, VPA, CLB, 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 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 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 or Sponsor safety representative/physician for review, which includes effects of study medication on seizures and comorbidities related to Dravet syndrome.

4. The Co-Chairs of the ICAB are alerted to the request, and in consultation with ERT prepare an evaluation of the risks and proposed monitoring plan if applicable for submission to the IDSMC/Sponsor safety representative/physician.
5. IDSMC/Sponsor safety representative/physician will review the submission from the Investigator and the ICAB.
6. IDSMC/Sponsor safety representative/physician 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
    d. Reduce the dose of study medication

When there is disagreement of findings in an ECHO of any subject between the ERT and ICAB (either in the alert level of valvular regurgitation or presence or absence of pulmonary hypertension), the following process will occur:

A telephone conference call will be held with the vendor ERT cardiology readers and ICAB reader and ICAB Chair (if the Chair was reader, then only s/he will be on call) to discuss and try to come to an agreement on interpretation; if agreement cannot be reached then the ICAB Chair will read the ECHO and his/her reading will become the official reading.

8.10. Pregnancy

This study is open to female and male subjects. Whenever possible, a pregnancy in a female subject 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 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.

A CRF 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 CRF via a secure internet connection. The investigator is responsible for ensuring accurate and proper completion of the CRF for recording data according to the instructions given in the CRF.

All entries in the CRF 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 (Section 12.8). Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

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

An optional subject's diary can be completed by the parent/caregiver at home. Data entries can be reviewed by the investigator for completion and consistency when performing the Seizure Assessment.

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 Sponsor or designee, 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 CRFs will be checked against the subject records for completeness and accuracy. The Sponsor's study monitor or designee will perform this function.

The computer system used for study data handling will be fully 21 Code of Federal Regulations (CFR) Part 11 compliant. All creation, modification or deletion of electronic study records will be documented through an automated Audit Trail. Following completion of CRF 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. Determination of Sample Size

The sample size will be determined by the number of subjects who participate in core studies Study ZX008-1503 or Study ZX008-1601 Part 2 and who volunteer for the extension study and meet the necessary criteria for enrollment. Up to 650 subjects may be eligible to participate in this extension study.

10.2. Analysis Populations

10.2.1. Safety (SAF) Population

Safety analyses will be performed on the Safety (SAF) Population defined as all subjects who receive at least 1 dose of ZX008 during this open label extension.

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

The modified Intent-to-Treat (mITT) Population is defined as all subjects who receive at least 1 dose of ZX008 and have at least 1 valid efficacy assessment during the open label extension. Effectiveness analyses, such as evaluating the improvement in seizure burden, will be performed on the mITT Population.

10.2.3. Per Protocol (PP) Population

The Per Protocol (PP) Population is defined as all subjects who receive at least 1 dose of ZX008, complete the entire OLE Treatment Period of this open label extension, and have no major protocol deviations that would have a significant impact on clinical outcome. Effectiveness analyses will be repeated on the PP Population in addition to the mITT Population.

10.3. Treatment Groups

All subjects will receive ZX008 and will be considered a single treatment group.

10.4. Treatment Periods

Pre-ZX008 Baseline Period

The pre-ZX008 baseline period is equivalent to the core study pre-randomization baseline period, ie, the approximately 42-day (Dravet syndrome) or 28-day (Lennox-Gastaut syndrome) span just prior to randomization and start of treatment in the double-blind studies.

Open-label Extension Treatment Period

The OLE Treatment Period covers the periodduring which subjects will receive open label treatment with ZX008 until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first .

Post-dosing Period

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

10.5. Statistical Analyses and Methods

All safety and effectiveness data will be summarized. 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 statistical analysis plan (SAP), which will be finalized before the database is locked.

10.5.1. Safety Analyses

Adverse events will be monitored throughout the open label extension. Adverse events will be considered to be treatment emergent (TEAE) if they begin between the first day of treatment with ZX008 and the last day of the Post-dosing period, or occur prior to first ZX008 treatment but increase in severity after ZX008 treatment begins.

The number and percentage of subjects in each treatment group with TEAEs will be displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). A table will enumerate the TEAEs that occur in at least 5% of subjects. A separate summary will be provided for all serious AEs (SAEs). Selected summaries will be repeated broken out by age group, ie, for ages <6 years; ≥6 years to <12 years; ≥12 years to <18 years; ≥18 years.

Physical examinations, vital signs, ECG, ECHO and body weight will be summarized appropriately. All safety summaries will be based on the SAF Population.

10.5.2. Effectiveness Analyses

10.5.2.1. Main Effectiveness Analysis

The main effectiveness endpoint is the CGI-I. The treating physician will rate their global impression of the patient's condition with the CGI-I throughout treatment with ZX008 according to the Schedule of Assessments. The severity of a patient's condition will be rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) by indicating the appropriate response that adequately describes how the patient's symptoms have improved or worsened relative to reference baseline CGI-S (Appendix 3) established at Visit 1. The CGI-I will be repeated by the parent/caregiver. The mean (SD) CGI-I score, and the number and percentage of subjects who showed improvement (ie, had a score of 3 or lower), or clinically meaningful improvement (ie, had a score of 2 or lower) will be presented for each assessment timepoint. Global CGI-I score and CGI-I score for cognition, behavior and motor abilities assessed by the principal investigator and parent/caregiver will be summarized and analyzed using the same methods, as described above. Investigators will also rate overall change in seizure frequency as <25%, ≥25%, ≥50%, or ≥75%, 100% (seizure-free) improvement compared to last visit.

10.6. 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 (neurology, cardiology, pediatrics, and statistics). The IDSMC members may request assistance from a number of additional and hoc members if needed. The oversight of safety and IDSMC responsibilities can be transferred back to the Sponsor's representative/study physician at any time.

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 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 a public database at (eg, ClinicalTrials.gov) in accordance with the local country requirements.

Before undergoing screening 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 CRF. 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. 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.

11.3. 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 CRF 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 subinvestigator(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 1 year after completion of the study, will be provided by the investigator and subinvestigator(s) to the Sponsor (delegate). All financial disclosure information provided by the investigator and subinvestigator(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 (eg, ClinicalTrials.gov) before or at commencement of the study, as required by local country requirements. 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 public databases (eg, 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 visit the study site to ensure adequacy of the facilities and to 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). This meeting will include an inventory of study supplies and a detailed review of the study protocol and procedures, the CRF, IMP accountability, and the subject diary if available.

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 CRFs, 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 CRF 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), 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 CRFs 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 CRF, 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 CRF. 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 and relevant medical records 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 CRF correctly and in a timely manner, after which the investigator will sign the CRF.

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.

13. REFERENCE LIST

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ZX008 Investigator's Brochure Version 6, March 8, 2018.

ZX008 Investigator's Brochure Version 8, 2020.

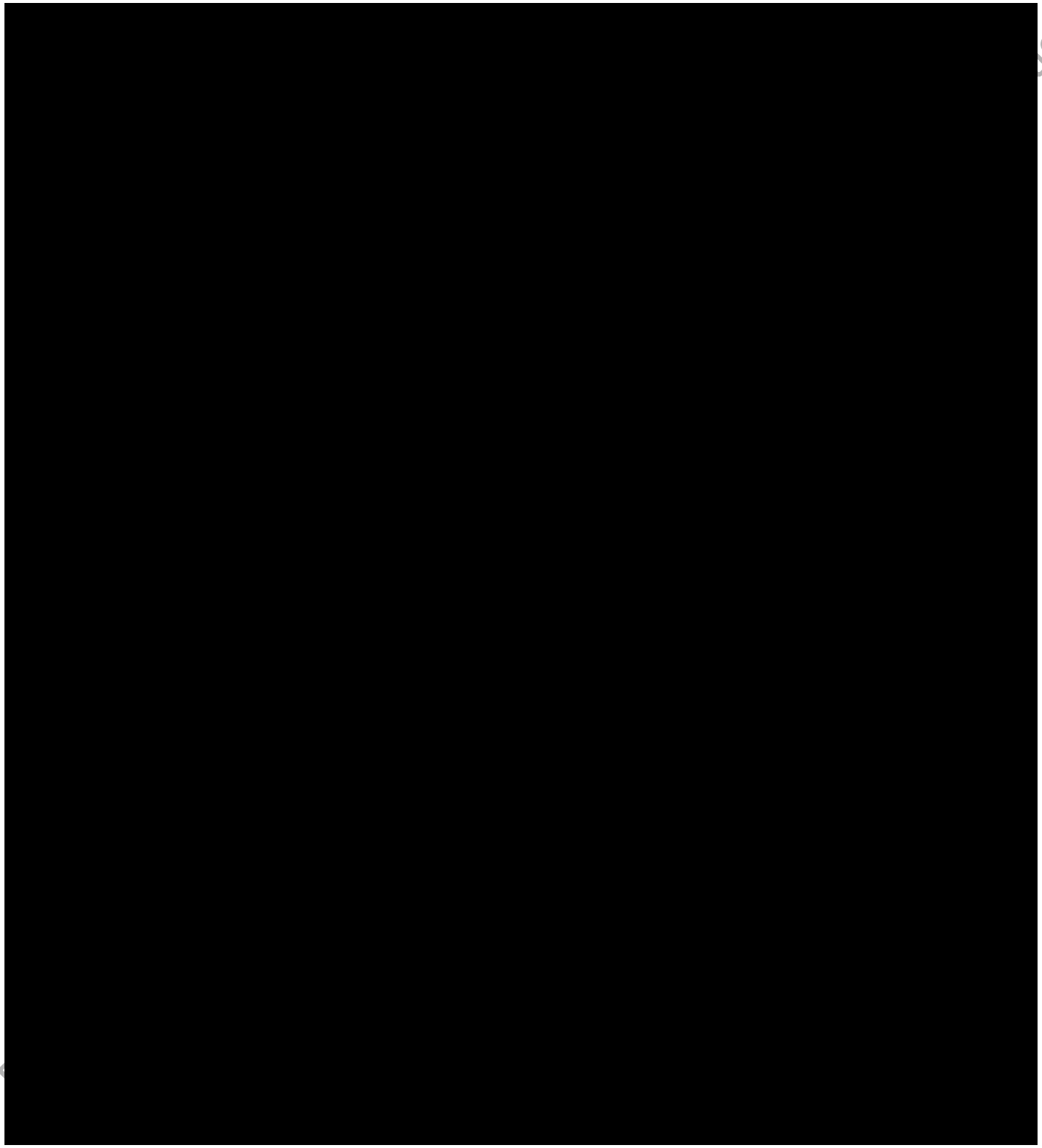
13.1. APPENDICES

Appendix 1 – List of Restricted Concomitant Medications

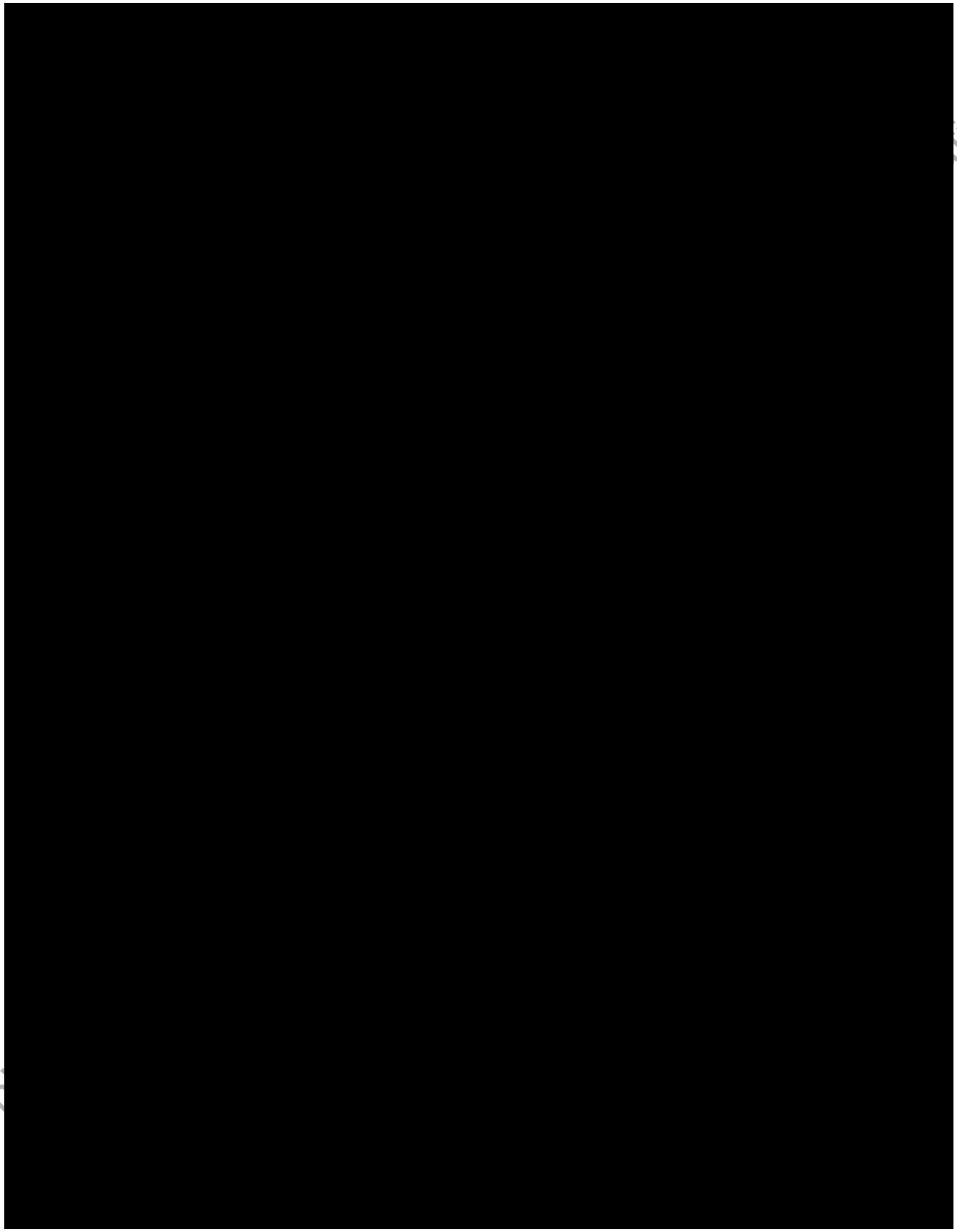
The below table lists examples of medications that should be avoided if possible as ongoing medications or for chronic use if initiated during the study from the time of signing the informed consent form (ICF) until the end-of-study visit (or early termination). If medical necessity requires the use of 1 or more of these medications during the course of the study, please contact the CRO Medical Monitor for approval.

ADHD Medications			
Amphetamine and derivates		Methamphetamine	Guanfacine
Methylphenidate	Dextroamphetamine	Lisdexamfetamine	Bupropion
Dexmethylphenidate	Clonidine		
Anti-arrhythmics	**Antibiotics**	**Anti-nausea**	**Anti-pyretic**
Mexiletine	Linezolid	Metoclopramide	Phenacetin
Propafenone		Ondansetron	
Anticonvulsants			
Retigabine/ezogabine			
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	Clonidine	Paliperidone	Risperidone
Amphetamine	Guanfacine	Perospirone	Sulpiride
Aripiprazole	Levomepromazine	Perphenazine	Ziprasidone
Asenapine	Methylphenidate	Promethazine	Zuclopenthixol
Clozapine	Olanzapine	Quetiapine	
Anti-viral	**Beta Blocker**	**Chemotherapy**	**Cough Suppressant**
Interferon	Alprenolol	Dasatinib	Dextromorphan
Ritonavir	Bufuralol		
Telaprevir			
Decongestants (allowed for short-term use only)		**Statins**	
Phenylpropanolamine		Cerivastatin	
Ergot Alkaloids, their derivatives, and Antiparkinson agents			
Pergolide	Cabergoline	Ergotamine Tartrate	
Opioids			
Alfentanil	Levacetylmethadol (LAAM)	Meperidine	Oxycodone
Codeine	Fentanyl	Methadone	Tramadol

13.2. Appendix 2 – Columbia – Suicide Severity Rating Scale



[redacted]



13.3. Appendix 3 – Clinical Global Impression – Severity (CGI-S)

Investigator Clinical Global Impression – Severity (to be completed at Visit 1)

Date completed (dd-mm-yr):___/____/____

GLOBAL

Circle the number that best rates the subject's condition overall relative to your clinical experience with this patient population.

1 = normal, not at all ill
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill

BEHAVIOR

Circle the number that best rates the subject's **overall behavior** relative to your clinical experience with this patient population.

1 = normal, not at all ill
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill

COGNITION

Circle the number that best rates the subject's **overall cognition** relative to your clinical experience with this patient population.

1 = normal, not at all ill
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill

MOTOR ABILITIES

Circle the number that best rates the subject's **overall motor ability** relative to your clinical experience with this patient population.

1 = normal, not at all ill
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill

Parent/Caregiver Clinical Global Impression – Severity (to be completed at Visit 1 via interview of the parent/caregiver)

Date completed (dd-mm-yr):___/____/____

GLOBAL

Circle the number that the parent/caregiver states best rates their impression of the subject's condition overall relative to their expectations for age and development.

1 = normal, not at all ill
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill

BEHAVIOR

Circle the number that the parent/caregiver states best rates their impression of the subject's **overall behavior** relative to their expectations for age and development.

1 = normal, not at all ill
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill

COGNITION

Circle the number that the parent/caregiver states best rates their impression of the subject's **overall cognition** relative to their expectations for age and development.

1 = normal, not at all ill
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill

MOTOR ABILITIES

Circle the number that the parent/caregiver states best rates their impression of the subject's **overall motor ability** relative to their expectations for age and development.

1 = normal, not at all ill
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill

13.4. Appendix 4 – Clinical Global Impression – Improvement (CGI-I)

Investigator Clinical Global Impression – Improvement

Date completed (dd-mm-yr):___/____/____

GLOBAL

Circle the number that best rates how subject's overall condition has improved or worsened relative to the rating provided at Visit 1.

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

BEHAVIOR

Circle the number that best rates how the subject's **overall behavior** has improved or worsened relative to the rating provided at Visit 1.

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

COGNITION

Circle the number that best rates how the subject's **overall cognition** has improved or worsened relative to the rating provided at Visit 1.

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

MOTOR ABILITIES

Circle the number that best rates how the subject's **overall motor ability** has improved or worsened relative to the rating provided at Visit 1.

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

Parent/Caregiver Clinical Global Impression – Improvement (to be completed via interview of the parent/caregiver)

Date completed (dd-mm-yr):___/____/____

GLOBAL

Circle the number that the parent/caregiver states best rates their impression of how the subject's overall condition has improved or worsened relative to the rating provided at Visit 1.

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

BEHAVIOR

Circle the number that the parent/caregiver states best rates their impression of how the subject's **overall behavior** has improved or worsened relative to the rating provided at Visit 1.

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

COGNITION

Circle the number that the parent/caregiver states best rates their impression of how the subject's **overall cognition** has improved or worsened relative to the rating provided at Visit 1.

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

MOTOR ABILITIES

Circle the number that the parent/caregiver states best rates their impression of how the subject's **overall motor ability** has improved or worsened relative to the rating provided at Visit 1.

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

13.5. Appendix 5 – Maximum Allowable Blood Draw Volumes

[redacted]

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)

[redacted]

13.6. Appendix 6 - 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:**

Visit 1 should be conducted in person. For Visits 2 through 6, 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, a "telemedicine visit" button will be available for selection on the overall visit page to capture the basis for missing or alternatively collected (i.e. 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
- Seizure assessment (by Investigator) when possible
- Scales and Questionnaires, when applicable and if feasible
    - C-SSRS
    - CGI-I (Global and Symptomatic, by Investigator and Parent/Caregiver)

3. End-of-Study/Early Termination (EOS/ET) and Follow-up Visits:

Cardiac follow-up visits must be conducted in-person.

For the EOS/ET visit and Post-Dosing Follow-up visits (ie, 2 weeks after the last dose), 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, these visits will be considered as missed.

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
- Seizure assessment (by Investigator) when possible

EOS/ET for subjects transitioning to Commercial drug:

For the EOS/ET visit (Visit 7) and Post-Dosing Follow-up visit (Visit 8), 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. Subjects who transition to commercially available drug must have had an ECHO within 3 to 6 months before the transition date. Subjects who transition to commercially available drug will have follow-up ECHOs within the required timeframe while on commercial drug.

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 assessments as described below, a documented risk/benefit discussion with the CRO 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 9 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 subject's need for travel. If the ECHO cannot be performed, a 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 Table8) the Cardiac Follow-up Visit may be skipped. If Level 2 or greater findings were observed, then the Cardiac Follow-up Visit should be re-scheduled 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 to be 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:

Laboratory assessments may be delayed up to 6 weeks. If further delay is required, and they are clinically indicated by the investigator, laboratory assessments may be conducted at local laboratory facilities. Local lab results are to be sent to the Principal Investigator for safety overread.

If results from the most recent assessments are within normal range or documented as clinically insignificant, further delays to obtaining laboratory assessments may be implemented based on clinical judgmental.

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.

13.7. Appendix 7- Summary of Protocol Amendment 4.0

Changes were made to protocol Amendment 3.1 to include updating the version number and date to Protocol Amendment 4.0 22 September 2022, as well as study number, sponsor signatories and affiliation, reflective its acquisition by UCB Pharma Inc. Language was modified to clarify how the end of study participation will occur. These changes required edits to the Synopsis, Schedule of Assessments, Sections 1.6, 3.1, 3.3, 6.1.3 and 10.4.

Further changes were made to the Synopsis, sections 3.7.1 and 4.4, 8.9.1 and 10.6 to reflect the opportunity to transfer of safety oversight back to the sponsor at any time during the study conduct.

Further updates were made to Section 1 to be updated with the newest information version of the ZX008 Investigator Brochure 2022 v10.0. Clarification was made on the affiliation of the study medical monitors throughout the document as well as on the result disclosure on public registries (Sections 2.3 and 8.5.1). Further changes included updating Section 8.6 to reflect the contact details for SAE reporting,

List of Specific Changes

Additions are marked in blue and red underline and deletions are marked in blue and red strikethrough. Minor editorial and non-substantive 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. Note that the list of specific changes below is presented in the order in which they first appear in the protocol, but several items are grouped by rationale.

<u>1. Updates were made to the Synopsis, Section 1.6, 3.1, 3.3, 6.1.3 and Section 10.4 concerning subjects end of study participation</u>

Synopsis:

STUDY SYNOPSIS

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome	
Study Number: ZX008-1900	
Study Product: Fenfluramine Hydrochloride Oral Solution, ZX008	
Type of Study: Long-term safety	**Indication(s) Studied:** Rare Seizure Disorders Such as Epileptic Encephalopathies, including Dravet syndrome and Lennox-Gastaut syndrome
Phase of Development: Phase III	**Countries:** North America, Europe, Australia, and Japan
Sponsor: Zogenix International Limited	
Co-Coordinating Investigator: [redacted]	
Estimated Duration of Individual Subject Participation: Participation for subjects will be voluntary until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects' country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first ~~up to 36 months or until ZX008 is approved in a subject's country of residence and listed on a patient's health plan formulary, whichever occurs first.~~	
Objectives: The primary objective of the study is: • To assess the long-term safety and tolerability of ZX008 The secondary objectives of the study are: • To assess the effect of ZX008 on the following effectiveness measures: – Investigator assessment of convulsive seizure response (<25%, ≥25%, ≥50%, ≥75%, or 100% [ie, seizure-free] improvement) – Clinical Global Impression – Improvement (CGI-I) rating, global and symptomatic, as assessed by the investigator – CGI-I rating, global and symptomatic, as assessed by the parent/caregiver	
Methodology: This is an international, multicenter, open-label, long-term safety study of ZX008 in patients with rare seizure disorders, epileptic encephalopathy, including Dravet syndrome or Lennox-Gastaut syndrome. Subjects eligible for participation are those with Dravet syndrome who are currently enrolled in Study ZX008-1503, or those with LGS who have successfully completed Study ZX008-1601-Part 2, and are candidates for continued treatment with ZX008 for an extended period of time, or those with Dravet syndrome, Lennox-Gastaut syndrome, or another epileptic encephalopathy who have completed participation in a Zogenix-sponsored study and have been invited to participate in this study. Participation in this OLE study is entirely voluntary Subject will be eligible to participate in this trial until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first ~~(for up to 36 months, or until ZX008 is approved in a subject's country of residence and listed on a patient's health plan formulary. Thus, the maximum duration for participation is 36 months.~~	

Duration of Treatment:

All subjects will receive ZX008 until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first. ~~for up to 36 months or until ZX008 is commercially available in a specific region, whichever occurs first.~~
All subjects who discontinue from the study treatment and do not transition directly to commercial product will undergo up to 2-weeks taper of study medication.

Section 1.6

1.6. Rationale for Current Study

As described above, Zogenix has conducted 2 positive double-blind, randomized, placebo-controlled studies in Dravet syndrome. Additionally, long-term safety and efficacy data for up to 3 years in some subjects has been collected. Based on the results from Study 1 and Study 1504 in Dravet syndrome, Zogenix has submitted a New Drug Application (NDA) to the United States Food and Drug Administration, and a Marketing Authorization Application (MAA) to the European Medicines Agency. Zogenix also has one double-blind placebo-controlled study ongoing in Lennox-Gastaut syndrome (Study 1601; NCT number:

NCT03355209). This is a 2-part study. Part 1 is a double-blind, parallel-group, placebo-controlled study to assess the efficacy and safety of 2 doses of ZX008 when used as adjunctive therapy for seizures in children and adult subjects with LGS. The primary study endpoint is

assessed from Part 1 data. Part 2 is a 1-year open-label, flexible-dose extension for subjects completing Part 1 of the study.

Study 1503 is soon to be completed, and Study 1601 Part 2 provideds treatment for up to 1 year. The main purpose of this open-label study is to continue to provide treatment to patients with Dravet syndrome or Lennox-Gastaut syndrome who may still derive clinically meaningful benefit from ZX008 after completing Study 1503 or Study 1601 Part 2, until the product is approved ~~and available via prescription~~, or a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first.

This study (1) additionally provides an opportunity to continue to evaluate the long-term safety of ZX008 in Dravet syndrome and Lennox-Gastaut syndrome until the product is approved and available via prescription; and, (2) may serve as an open-label extension study for patients with rare seizure disorders and epileptic encephalopathies who have participated in other Zogenix-sponsored clinical trials of ZX008.

Section 3.1

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is an international, multicenter, open-label, long-term safety study of ZX008 in patients with epileptic encephalopathy, including Dravet syndrome or Lennox-Gastaut syndrome. Subjects eligible for participation are those with Dravet syndrome who are currently enrolled in Study ZX008-1503, or those with Lennox-Gastaut syndrome who have successfully completed Study ZX008-1601-Part 2, and are candidates for continued treatment with ZX008 for an extended period of time, or those with Dravet syndrome, Lennox-Gastaut syndrome, or another epileptic encephalopathy who have completed participation in another Zogenix-sponsored study and have been invited to participate in this study.

~~Dravet s~~Subjects~~,~~ having transitioned from ZX008-1503, ZX008-1601 or ~~-~~who have participated in another Zogenix-sponsored study~~,~~ will be eligible to participate in this trial until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first~~ for up to 36 months, or until ZX008 is approved in the subject's country of residence and listed on a patient's health plan formulary~~.

~~LGS subjects, having transitioned from ZX008-1601 will be eligible to participate in this trial for up to 36 months, or until ZX008 is approved in a subject's country of residence and listed on a patient's health plan formulary.~~

~~Subjects who have participated in another Zogenix sponsored study will be eligible to participate in this trial for up to 36 months, or until ZX008 is approved in the subject's country of residence and listed on a patient's health plan formulary.~~

All subjects who discontinue from the study treatment and do not transition directly to commercial product will undergo up to 2-weeks taper of study medication. (Note subjects enrolled in the United Kingdom will have an additional follow-up safety visit 12 months after the last dose; subjects enrolled in Germany, France, and Netherlands will have an additional follow-up safety visit at 24 months after the last dose).

Section 3.3

3.3. Study Duration

~~Dravet s~~Subjects~~,~~ having transitioned from ZX008-1503, ZX008-1601 or who have participated in another Zogenix-sponsored study, will be eligible to participate in this trial until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first~~ for up to 36 months, or until ZX008 is approved in the subject's country of residence and listed on a patient's health plan formulary~~.

~~LGS subjects, having transitioned from ZX008-1601 will be eligible to participate in this trial for up to 36 months, or until ZX008 is approved in a subject's country of residence and listed on a patient's health plan formulary.~~

~~Subjects who have participated in another Zogenix sponsored study will be eligible to participate in this trial for up to 36 months, or until ZX008 is approved in the subject's country of residence and listed on a patient's health plan formulary.~~

Section 6.1.3:

6.1.3. Clinic Visit 7 (Month 36): End of Study/Early Termination

The End-of-Study participation for an individual subject occurs ~~after he/she has received IMP for up to 3 years in this OLE study Treatment Period, or~~ when approval of ZX008 has been obtained from regulatory authorities for the subject's indication, when a managed access program is

established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or when the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first. In that regard, participation could be extended beyond 36 months if none of the conditions above mentioned are met at Visit 7.

~~ZX008 is approved in a subject's country of residence and listed on a patient's health plan formulary, whichever occurs first~~. The End-of-Study visit may also occur if the subject withdraws participation from the study ~~or the Sponsor terminates the study~~.

Subjects will visit the clinic for the End-of-Study Visit if 1 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.
4. ZX008 is approved by regulatory authorities for the subject's indication, a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first ~~in a subject's country of residence and is listed on a patient's health plan formulary~~

Section 10.4:

10.4. Treatment Periods

Pre-ZX008 Baseline Period

The pre-ZX008 baseline period is equivalent to the core study pre-randomization baseline period, ie, the approximately 42-day (Dravet syndrome) or 28-day (Lennox-Gastaut syndrome) span just prior to randomization and start of treatment in the double-blind studies.

Open-label Extension Treatment Period

The OLE Treatment Period covers the period~~the 36 months~~ during which subjects will receive open label treatment with ZX008 until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subjects country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first .

2. Updates were made to the Synopsis, sections XX and XX to reflect the opportunity to transfer of safety oversight back to the sponsor at any time during the study conduct

Synopsis:

External Committees: The ZX008 clinical program will employ an Independent Data and Safety Monitoring Committee (IDSMC) that will be responsible for safety oversight until the safety oversight is transferred back to the Sponsor or the drug is approved in a major market for the studied indications. A separate International Cardiology Advisory Board (ICAB) will monitor the cardiac safety of the ZX008 clinical trials. ECHOs will be centrally read (ERT, Inc.) and interpreted using pre-specified criteria, and if necessary, with review by the ICAB.

Section 3.7.1:

3.7. Study Monitoring Procedures

3.7.1. Independent Data and Safety Monitoring Committee (IDSMC)

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

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

The IDMSC will:

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

The responsibilities of the IDSMC on the safety oversight can be transferred back to the Sponsor at any time during the course of the study.

Section 4.4:

4.4. 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 CRF. 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:

1. Development of signs or symptoms indicative of cardiac valvulopathy or regurgitation (mitral, aortic, tricuspid, pulmonary valves), or pulmonary hypertension for which IDSMC or the Sponsor, in consultation with the ICAB, the central cardiac reader, and the investigator believe the benefit of continued participation does not outweigh the risk.

10. It is the investigator's or Ssponsor's opinion that it is not in the subject's best interest to continue in the study.
11. 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. Discontinuation decisions due to development of cardiovascular or cardiopulmonary complications may be made by the IDMSC or the Sponsor, with input from the ICAB and the investigator.

If feasible, the process of discontinuation should be discussed with the CRO 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 CRO Medical Monitor, but final decisions about the process will remain at the discretion of the site principal investigator.

Section 8.9.1:

must sign a new consent which describes the additional risk 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 or Sponsor safety representative/physician for review, including consideration of effects on seizures and comorbidities.
4. The Co-Chairs of the ICAB are alerted to the request and prepare, after consultation with an evaluation of the cardiopulmonary risk and proposed monitoring plan if applicable, for submission to the IDSMC or Sponsor safety representative/physician.
5. IDSMC/Sponsor safety representative/physician will review the submission from the Investigator and the ICAB.
6. IDSMC/Sponsor safety representative/physician 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 if available and consult with the parent/guardian, and determine whether the achieved benefit justifies the consideration of continuing study treatment by the IDSMC/Sponsor safety representative/physician. Minimal efficacy criteria for IDSMC/Sponsor safety representative/physician consideration:

a. Seizures must be more than 75% improved (number of convulsive 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, VPA, CLB, 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 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 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 or Sponsor safety representative/physician for review, which includes effects of study medication on seizures and comorbidities related to Dravet syndrome.

4. The Co-Chairs of the ICAB are alerted to the request, and in consultation with ERT prepare an evaluation of the risks and proposed monitoring plan if applicable for submission to the IDSMC/Sponsor safety representative/physician.
5. IDSMC/Sponsor safety representative/physician will review the submission from the Investigator and the ICAB.
6. IDSMC/Sponsor safety representative/physician 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
    d. Reduce the dose of study medication

Section 10.6:

10.6. 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 (neurology, cardiology, pediatrics, and statistics). The IDSMC members may request assistance from a number of additional and hoc members if needed. The oversight of safety and IDSMC responsibilities can be transferred back to the Sponsor's representative/study physician at any time.

3. Section 1 was updated with the newest information and version of ZX008 Investigator Brochure 2022. The Reference List was also updated to include Investigator Brochure version 10.0.

1.1.1. Existing Treatment for Dravet Syndrome

Diacomit® (stiripentol) was recently approved in the United States, and has been approved for many years in Canada, Europe, and Japan to treat seizures associated with Dravet syndrome. Stiripentol (STP) must be co-administered with clobazam (US label) or clobazam and valproate (ex-US label). STP can significantly impact plasma concentrations of other AEDs, most notably clobazam. The complex drug-drug interactions of STP with other medications requires close monitoring and close management of side effects.

Fintepla® and Epidiolex® (cannabidiol) has recently been approved by the FDA and EMA (Fintepla®, Epidyolex®) for the treatment of seizures associated with Dravet syndrome.

Other therapies, topiramate, levetiracetam, and bromide may provide efficacy as adjunctive therapy for some patients (Chiron 2011). Published uncontrolled studies with levetiracetam (Striano 2007), verapamil (Iannetti 2009), ketogenic diet (KD) (Caraballo 2011a; Caraballo 2011b), deep brain stimulation (Andrade 2010), and vagal nerve stimulation (VNS) (Zamponi 2011) show infrequent clinically meaningful improvement. Carbamazepine, oxcarbazepine, lamotrigine, phenytoin, vigabatrin, and high doses of intravenous phenobarbital should be avoided because they often exacerbate seizures (Sazgar 2005; Wirrell 2016; de Lange 2018). Rescue medications (clonazepam, diazepam, lorazepam, and midazolam, etc) are often used to stop prolonged seizures that may evolve to SE and require emergency intervention.

1.1.2. Existing Treatment for Lennox-Gastaut Syndrome

Currently, there are ~~7~~ 8 approved anti-epileptic drug (AED) products for LGS in the US: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, ~~and~~ cannabidiol (Epidiolex®) and fenfluramine (Fintepla®). 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) and seizures in LGS are usually not fully controlled (Hancock 2013). Initial treatment for LGS is usually monotherapy with 1 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

1.4. Clinical Pharmacology

Please see the ZX008 IB for details on clinical pharmacology (ZX008 IB 2022 v10.0). Below are the clinical pharmacology conclusions.

4. Updates were made to Sections 2.3 and 8.5.1 to clarify the result disclosure on public registries.

Section 2.3:

2.3. Study Endpoints

2.3.1. Safety Endpoints

The safety endpoints of the study are:

- AEs
- Laboratory safety (hematology, chemistry)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Physical examination
- Neurological examination
- Electrocardiogram (ECGs)
- Doppler echocardiogram (ECHOs)
- Body weight/height
- Chest x-ray (subjects in France and Netherlands only)
- Electroencephalogram (EEG) (in Italy only)

Laboratory safety parameters (hematology, chemistry), ECGs, EEGs (in Italy only), and chest-x-ray (in France and Netherlands only), will only be assessed as clinically indicated.

For results disclosure on public registries (e.g. ClinicalTrials.gov and EudraCT), only incidence of TEAEs will be publicly disclosed as a Primary Endpoint. The remaining Safety Endpoints are considered as other for the purpose of public data disclosure.

Section 8.5.1:

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 CRF. 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 CRF.

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

5. Section 8.6 was updated to reflect the current contact details for SAE Reporting.

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:

All SAEs that occur during the course of the study, beginning at Visit 1, whether or not causally related to IMP must be reported immediately via telephone or email or EDC (within 24 hours of the investigator becoming aware of the event) to the Sponsor or the CRO Medical Monitor.

1. Enter all relevant information into SAE eCRF, via the EDC.
2. In the event that EDC is down or not accessable the site can send a paper SAE form to the Safety team within 24 hours of becoming aware of the SAE and then enter the SAE into the eCRF page once the EDC is back up and accessible.

Adverse events occurring in the period between the time the subject gave written informed consent and the first exposure to IMP that meet 1 or more of the seriousness criteria for AEs must be reported to the Ssponsor and the CRO 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 and the CRO Medical Monitor**.

Contact details and guidance for reporting SAEs ~~will be provided to study site before the study starts~~ are provided below:

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com