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 in Children and Young Adults with Dravet Syndrome
Study Number:	ZX008-1503
Study Product:	Fenfluramine Hydrochloride Oral Solution; ZX008
IND Number:	125797
EudraCT:	2016-002804-14
Sponsor:	Zogenix International Limited A wholly owned subsidiary of Zogenix, Inc. 5959 Horton Street, [redacted] Emeryville, CA 94608 USA
Sponsor's Medical Contact	[redacted] Zogenix, Inc.
Date/Version of Study Protocol:	03 August 2020 (amendment 5.0: ROW) 02 February 2018 (amendment 4.0: ROW) 05 May 2017 (amendment 3.0: ROW) 01 November 2016 (amendment 2.0: ROW) 13 September 2016 (amendment 1.2.1: ROW) 31 May 2016 (amendment 1.2: ROW) 07 March 2016 (original)

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF STUDY

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

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SIGNATURE OF SPONSOR

Study Number: ZX008-1503

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

Sponsor's Responsible Officer: [redacted]

[redacted]

Zogenix International Limited
A wholly owned subsidiary of Zogenix, Inc.
5959 Horton Street, [redacted]
Emeryville, CA 94608 USA

[redacted]

(Signature)

10/8/2020

(Date [DD/MMM/YYYY])

SIGNATURES OF CO-COORDINATING INVESTIGATORS

Study Number: ZX008-1503

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

Co-Coordinating Investigator:

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[redacted] Pediatric Epilepsy Center
University of California, San Francisco
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[redacted]

06 Aug 2020

SIGNATURES OF CO-COORDINATING INVESTIGATORS

Study Number: ZX008-1503

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

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Co-Coordinating Investigator: [redacted]

Leuven University, Department of Development and Regeneration, Section Pediatric Neurology
Leuven, Belgium

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07 AUG 2020

(Date [DD/MMM/YYYY])

SIGNATURES OF CO-COORDINATING INVESTIGATORS

Study Number: ZX008-1503

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet Syndrome

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[redacted] 10 AUG 2020

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

SIGNATURE(S) OF PRINCIPAL INVESTIGATOR(S)

Study Number: ZX008-1503

Study Title: An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy in Children and Young Adults with Dravet 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
ADHD	attention deficit hyperactivity disorder
AE	adverse event
AED	antiepileptic drug
AESI	adverse event of special interest
ANCOVA	analysis of covariance
BID	bis in die; two times per day
BMI	body mass index
BRIEF	Behavior Rating Inventory for Executive Function
CBD	cannabidiol
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression - Improvement
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
dL	deciliter
DS	Dravet syndrome
ECG	electrocardiogram
ECHO	echocardiogram
EOS	end of study
EQ-5D-5L	standardized measure of health status
ET	early termination
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GH	growth hormone
GMP	Good Manufacturing Practices
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HR	heart rate
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
IPCAB	International Pediatric Cardiology Advisory Board

ABBREVATION	DEFINITION
IRB	Institutional Review Board
IVR	interactive voice response (system)
IWR	interactive web response (system)
KD	ketogenic diet
kg	kilogram
LH	luteinizing hormone
LLN	lower limit of normal
MCSF	mean convulsive seizure frequency
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg/day	milligram per kilogram per day
min	minutes
mITT	modified Intent to Treat
mL	milliliter
OLE	open-label extension
PedsQL	Pediatric Quality of Life Inventory
PDN	Postnatal day
PP	per protocol
QoL	quality of life
QOLCE	Quality of Life in Childhood Epilepsy
QTcF	corrected QT interval using Fredericia method
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SE	status epilepticus
SMEI	severe myoclonic epilepsy of infancy
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy
THC	tetrahydrocannabinol
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 in Children and Young Adults with Dravet Syndrome

Study Number: ZX008-1503

Study Product: Fenfluramine Hydrochloride, ZX008

Type of Study:	**Indication Studied:**
Safety and effectiveness study	Adjunct therapy in Dravet syndrome
Phase of Development: Phase III	**Countries:** North America, Europe, Australia

Sponsor: Zogenix International Limited

Co-Coordinating Investigators:

[redacted] Pediatric Epilepsy Center University of California, San Francisco San Francisco, CA USA	[redacted] Leuven University, Department of Development and Regeneration, Section Pediatric Neurology Leuven, Belgium	[redacted] Service de Neurométabolisme CHU Paris - Hôpital Necker-Enfants Malades Paris, France

Estimated Duration of Individual Subject Participation:
The duration of the study for an individual subject is expected to be up to approximately 36 months.

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 relative to the pre-ZX008 baseline on the following effectiveness measures:
  - The change in the frequency of convulsive seizures from Visit 3 to Visit 8 (ie, Day 31 to Day 365) and for the entire Year 1 treatment period (ie, Visit 1/Day 1 to Visit 8/Day 365)
  - The proportion of subjects who achieve a ≥ 40%, ≥ 50%, and ≥ 75% reduction in convulsive seizure frequency
  - The longest convulsive seizure-free interval
  - The percentage of convulsive seizure-free days
  - The non-convulsive seizure frequency
  - The convulsive + non-convulsive seizure frequency.
- To estimate the incidence of the following on subjects receiving ZX008:
  - Use of rescue medication
  - Hospitalization to treat seizures
  - Status epilepticus (SE)
- To assess the effect of ZX008 relative to the pre-ZX008 baseline on the following quality of life (QoL) measures:
  - Quality of Life in Childhood Epilepsy (QOLCE) score
  - Pediatric Quality of Life Inventory™ (PedsQL) score
  - PedsQL Family Impact module score
  - QoL of the parent/caregiver using the standardized measure of health status (EQ-5D-5L) scale
  - Affective symptoms of the parent/caregiver using the Hospital Anxiety and Depression Scale (HADS)

- To assess the effect of ZX008 on the following QoL measures:
  - Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the principal investigator
  - CGI-I rating, as assessed by the parent/caregiver

The exploratory objectives of the study are:

- To assess the effect of ZX008 on the following QoL measures for subjects who participated in the core study ZX008-1504:
  - Sleep quality and mealtime behavior, as assessed by the parent/caregiver
  - Karolinska Sleep Scale
  - Health and social care resource use (These measures include planned and unplanned hospital visits, use of ambulances, general practitioner [GP] visits, speech and language therapy utilization, occupational and physical therapy utilization).

Methodology: This is an international, multicenter, open-label, long-term safety study of ZX008 in pediatric and young adult subjects with Dravet syndrome (DS). Subjects eligible for participation are those who have successfully completed 14 weeks of treatment in 1 of the 3 core studies ZX008-1501, ZX008-1502, or ZX008-1504 Cohort 2, or successfully completed core study ZX008-1504 Cohort 1 and are candidates for continuous treatment for an extended period of time. In addition, subjects who are >18 to ≤35 years of age at the time of screening, and who meet all other eligibility criteria may be eligible for participation after discussion with the Medical Monitor and sponsor about the potential risks and benefits for receiving ZX008. Participation for these subjects will be at the discretion of the sponsor.

This trial will consist of an up to 36-month Open-Label Extension (OLE) Treatment Period and a 2-week Post-Dosing Period. Thus, subjects who complete this trial will have been treated with ZX008 for a minimum of up to 3 years (including their participation in both the core study and this study). Subjects who did not participate in one of the core studies will undergo a screening period up to 28 days to confirm eligibility prior to receiving their first dose in the OLE Treatment Period.

During the OLE Treatment Period, all subjects will be treated initially with 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study subjects. After 1 month at a dose of 0.2 mg/kg/day, the investigator may adjust the dose of each subject based on effectiveness and tolerability. For subjects who are not receiving concomitant stiripentol (STP), including de novo subjects and those who participated in core studies ZX008-1501, Z008-1502, and dose regimen 1 or 2 from Cohort 1 of ZX008-1504, dose changes should be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day. For subjects who are receiving concomitant STP, including de novo subjects and those who participated in core study ZX008-1504 Cohort 1, dose regimen 3 and Cohort 2, 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 should not occur earlier than every 14 days at each dose level. Dose increases may only occur after a review of the diary and reported 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 can occur at the investigator's discretion, in dose amounts and frequency appropriate for the situation. ZX008 dose adjustments outside of these parameters should be discussed with the Medical Monitor prior to initiation.

In addition, if a subject has been stable on the same dose of ZX008 for 6 months or longer, investigators may adjust the doses of one or more of the other concomitant anti-epileptic drugs (AEDs) as per typical clinical practice. Concomitant AEDs may be withdrawn completely but all subjects must remain on a minimum of 1 concomitant AED plus ZX008. No new concomitant AEDs or anti-epileptic treatments may be introduced while in this study. All medication dose changes must be documented with a clinical explanation and justification. Concomitant AED dose adjustments outside of these parameters should be discussed with the Medical Monitor prior to initiation if possible.

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

A follow-up electrocardiogram (ECG) and echocardiogram (ECHO) will be performed at 3 and 6 months after study drug discontinuation for early termination and for those subjects who complete the study. Caregivers will use a diary daily to record the number/type of seizures, dosing, and use of rescue medication. A schedule of assessments is provided in **Table 1** for subjects from core studies ZX008-1501 and ZX008-1502 and those who did not participate in one of the core studies (de novo subjects), and in Table 2 for subjects from core study ZX008-1504.

After at least 1 year of treatment in Study 1503 subjects who participated in one of the core studies will transition to a separate extension study (Study 1900) once that study is approved and the study site is initiated. Continuation in a separate extension protocol will be based on benefit/risk and continued eligibility criteria being met. De novo subjects must have participated in this trial for at least 3 months with at least 1 ECHO completed and continue to meet eligibility requirements to be eligible to transition to a separate extension protocol. Alternatively, subjects will transition to commercial product once it is available. For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial. Subjects who transition to commercially available drug must have an ECHO within 3-6 months before starting commercial drug and will have follow-up ECHOs within the required timeframe while on commercial drug.

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

Number of Subjects: Up to approximately 340 subjects from the core studies and up to 50 subjects who did not participate in 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 aged 2 to 18 years inclusive, as of the day of the core study Screening Visit.
2. Subject has satisfactorily completed the core study in the opinion of the investigator and the Sponsor. NOTE: Those subjects who do not complete the 12-week Maintenance Period of the core study may, on a case-by-case basis, be eligible for entrance after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a ZX008 trial. The decision whether to permit OLE study participation resides solely with the Sponsor, who may consult with the site investigator, the IPCAB and/or the IDSMC.
3. Subject is male or non-pregnant, non-lactating female. Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative urine pregnancy test. 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 documented medical history to support a clinical diagnosis of DS, where convulsive seizures are not completely controlled by current antiepileptic drugs.
5. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
6. Subject has provided assent in accordance with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements, if capable.
7. Subject's caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.
8. Subject's parent/caregiver has been compliant with diary completion during the core study, in the opinion of the investigator (eg, at least 90% compliant).
9. Subjects entering from study ZX008-1504 must be receiving a therapeutically relevant and stable dose of clobazam (CLB) and/or valproic acid (VPA), and STP (Cohort 1 dose regimen 3 and Cohort 2 only) for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
10. Subjects who are >18 to ≤35 years of age at the time of screening and did not participate in one of the core studies must meet criteria 3 to 7 above and the following criteria below in order to be considered for participation. Participation is at the discretion of the Sponsor:
    a. Onset of seizures in the first year of life in an otherwise healthy infant.
    b. A history of seizures that are either generalized tonic-clonic or unilateral clonic or bilateral clonic, and are prolonged.
    c. Initial development is normal.
    d. History of normal brain MRI without cortical brain malformation.
    e. Lack of alternative diagnosis.
    f. Meets one of the following 3 confirmatory diagnostic criteria:
        i. Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal has developed after the first seizure type.
        ii. Prolonged exposure to warm temperatures induces seizures and/or seizures are associated with fevers due to illness or vaccines, hot baths,

high levels of activity and sudden temperature changes and/or seizures are induced by strong natural and/or fluorescent lighting, as well as certain visual patterns.

iii. Genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis.)

g. Subject has been approved for study inclusion by the Epilepsy Study Consortium.

h. Subject does not have an exclusionary cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination and is approved for entry by the central cardiac reader. Exclusionary abnormalities include, but are not limited to:
   i. Mild or greater mitral or aortic valve regurgitation in subjects >18 yrs of age
   ii. Possible signs of pulmonary hypertension with abnormal or greater than upper limit of normal values
   iii. Evidence of diastolic dysfunction

i. Subject must have had ≥4 convulsive seizures (tonic, tonic-atonic, tonic-clonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.

j. All medications or interventions for epilepsy (including ketogenic diet [KD] and vagal nerve stimulation [VNS]) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.

11. Subject's parent/caregiver is willing and able to be compliant with diary completion, 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 or past history of cardiovascular or cerebrovascular disease, myocardial infarction or stroke.

3. Subject from one of the core studies with current cardiac valvulopathy or pulmonary hypertension that the investigator, parent, IPCAB, IDSMC, or Sponsor deems clinically significant and warrants discontinuation of study medication.

4. For de novo subjects: possible signs of pulmonary hypertension with abnormal or greater than upper limit of normal values.

5. Subject has current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month.

6. 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.

7. Subject has a current or past history of glaucoma.

8. 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 Medical Monitor in conjunction with the Sponsor, in consideration of comorbidities and concomitant medications.
9. Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; cyproheptadine, and/or cytochrome P450 (CYP) 2D6/3A4/2B6 inhibitors/substrates (Appendix 1). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)
10. Subject is currently taking carbamazepine, oxcarbazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy.
11. For subjects entering from core studies ZX008-1501, ZX008-1502, or ZX008-1504 (Cohort 1/dose regimens 1 &2): Subject is currently receiving or has received stiripentol in the past 21 days prior to core study Visit 1.
12. Subject is unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges, and their juices beginning with the Visit 1 and throughout the study.
13. Subject has positive result on urine tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at Visit 1.
14. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
15. 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.
16. Subject has participated in another clinical trial within the past 30 days (ie, the last visit of the previous study was in the past 30 days), with the exception of one of the core studies.

Study Product, Dose, and Mode of Administration:

- ZX008 is supplied as an oral solution in a concentration of 2.5 mg/mL. Subjects will be titrated to an effective dose beginning with 0.2 mg/kg/day (maximum 30 mg/day for subjects who are not receiving concomitant STP; maximum 20 mg/day for subjects who are receiving concomitant STP). Study medication will be administered twice a day (BID) in equally divided doses with food.

Reference Product, Dose, and Mode of Administration:

Not applicable.

Duration of Treatment:

All subjects will receive ZX008 for up to approximately 36 months. All subjects, including those who prematurely discontinue from the study, will undergo an up to 2-week taper of study medication, at the conclusion of the study.

Criteria for Evaluation:

Safety:

AEs, laboratory safety parameters (hematology, chemistry, urinalysis), vital signs (blood pressure, heart rate, temperature, and respiratory rate), physical examination, neurological examination, 12-lead ECGs, Doppler ECHOs, and body weight. The Behavior Rating Inventory for Executive Function (BRIEF) will be administered to track cognitive function.

Effectiveness:

- Number of seizures by type
- Convulsive seizure-free interval
- CGI-I as assessed by parent/caregiver
- CGI-I as assessed by principal investigator
- QOLCE to measure changes in quality of life of the subject
- PedsQL to measure changes in quality of life of the subject
- PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver
- QoL of parent/caregiver using the EQ-5D-5L scale
- Affective symptoms of parent/caregiver using the Hospital Anxiety and Depression Scale (HADS) (in parents/caregivers from core studies ZX008-1501 and ZX008-1502 only)
- Duration of prolonged seizures (seizure type that, during pre-ZX008 baseline, had duration > 2 minutes)
- Number of episodes of SE
- Number of instances of rescue medication use and number of doses
- Number of inpatient hospital admissions due to seizures

Exploratory (in subjects who participated in core study ZX008-1504 only):

- Health and social care resource use, including GP visits, speech and language, occupational and physical therapy, in addition to acute hospital and institutional length of stay, loss of work, etc.
- Sleep quality
- Mealtime behavior
- Karolinska Sleepiness Scale to measure the effect of study medication on sleepiness

Sample Size Determination:

The sample size will be determined by the number of subjects who participate in 1 of the 3 core studies – Study ZX008-1501, Study ZX008-1502, or ZX008-1504 - and who volunteer for the extension study and meet the necessary criteria for enrollment. Approximately 100-120 subjects are expected to participate in each of the core trials; thus, if all participants also enroll in the extension, the total sample size of the extension trial would be up to approximately 340. In addition, up to 50 additional subjects, who otherwise would have qualified for participation in one of the core studies, but are >18 to ≤35 years of age may participate.

Statistical Methods:

Study Populations

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

Modified Intent-to-Treat (mITT) Population: The mITT Population is defined as all subjects who receive at least one dose of ZX008 and have valid seizure data during the open label extension.

Safety

The number and percentage of subjects who experience treatment emergent AEs will be displayed by body system and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries in terms of severity and relationship to study drug will also be provided. Serious AEs

(SAEs) will be summarized separately in a similar manner. Laboratory tests, vital signs, physical examinations, neurological examinations, ECG, ECHO, cognition and body weight will be summarized using appropriate methods.

Effectiveness

The frequency of convulsive seizures during a given treatment period will be derived from the number and type of events recorded in subject diaries. The seizure frequency per 28 days will be calculated as the number of seizures recorded divided by the number of days in the period and multiplied by 28. The convulsive seizure frequency during the OLE Treatment Period will be compared to the pre-ZX008 baseline frequency measured prior to first treatment with ZX008. Both the mean and median change from baseline will be presented and the statistical significance of the change will be assessed using an analysis of covariance (ANCOVA) with baseline frequency as a covariate and age group (< 6 or ≥ 6 years old) as a factor. Other factors may be included in the model if they are found to be informative during analyses of the core trials. Similar methods will be used to assess the change in frequency of non-convulsive seizures and the composite endpoint of non-convulsive plus convulsive seizures. The percentage of subjects who achieve a ≥ 40%, ≥ 50%, and ≥ 75% reduction in seizures will be presented along 95% confidence intervals for each percentage. Quality of life measures, such as the QOLCE assessed during the OLE Treatment Period, will be compared to the analogous baseline measure assessed prior to first treatment with ZX008. Subjects who did not participate in one of the core studies will be excluded from analyses of effectiveness and the change over time will be described.

Table 1. Schedule of Assessments for Subjects from Core Studies ZX008-1501 and ZX008-1502, and de Novo Subjects**

Study Assessments	**OLE Treatment Period**					**Post-Dosing**	**Cardiac Follow-up**
Visit Number	**Visit 1[a]**	**Visit 2[c]**		**Visits 3-15 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33)**	**Visit 16[d] (EOS/ET) Month 36**	**Visit 17[o]**	**Visit 18, 19[o]**
Study Day	**-28 to 1[a]**	**15**		**30, 60, 90, 180, 270, 365, 455, 545, 635, 725. 815, 905, 995**	**1085**	**1099**	**3 and 6 months post last dose**
		Clinic	**Phone**				
Informed Consent	X						
Entry Criteria	X						
Demographics	X						
Medical/Neurological History	X[a]						
Epilepsy History	X[a,b]						
Physical Examination, complete	X[a]				X		X[e]
Physical Examination, abbreviated		X		X			X[e]
Neurological Examination, complete	X[f]				X		
Neurological Examination, abbreviated		X		X			
Vital signs	X	X		X	X		
Weight, Height, BMI	X[a]	X		X	X		
12-lead ECG	X[a]			X	X		X[e]
Doppler ECHO	X[a]			X[g,h]	X		X[e]
Urine Pregnancy Test[h]	X			X	X		
Clinical laboratory evaluation (hematology/clinical chemistry/urinalysis, etc)	X[j]	X[j]		X	X		
Urine THC Panel/Whole blood CBD	X[a]			X	X		
Plasma sample for background AEDs		X		X	X		
Tanner Staging (for subjects >7 to ≤ 18 years)	X[a]			X[k]	X		X[k]
C-SSRS	X[a]			X	X		
CGI-I (assessed by parent/caregiver)	X[a]			X	X		
CGI-I (assessed by principal investigator)	X[a]			X	X		
QOLCE	X[a]			X	X		
EQ-5D-5L (QoL of parent/caregiver)	X[a]			X	X		
HADS (Affect of parent/caregiver)	X[a]			X	X		
BRIEF	X[a]			X	X		

continued

Table 1. Schedule of Assessments for Subjects from Core Studies ZX008-1501 and ZX008-1502, and de Novo Subjects** (continued)

Study Assessments	OLE Treatment Period					Post-Dosing	Cardiac Follow-up
Visit Number	**Visit 1[a]**	**Visit 2[c]**		**Visits 3-15 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33)**	**Visit 16[c] (EOS/ET) Month 36**	**Visit 17[o]**	**Visit 18, 19[o]**
Study Day	**-28 to 1[a]**	**15**		**30, 60, 90, 180, 270, 365, 455, 545, 635, 725. 815, 905, 995**	**1085**	**1099**	**3 and 6 months post last dose**
		Clinic	**Phone**				
PedsQL [n]	X[a]			X	X		
Study medication palatability assessment				X[l]			
Subject Diary	D	C/R/D	R	C/R/D	C/R	C/R	
Study Medication	D[b]	C/R/D	R	C/R/D	C/R/D	C/R	
Daily Diary Completion	---------- X ----------						
Concomitant Medication	X[a]	---------- X ----------					
Adverse Events	X[a]	---------- X ----------					
Adverse events of special interest	X[a]	---------- X ----------					X[m]

AED=antiepileptic drug; BMI=body mass index; BRIEF=Behavior Rating Inventory of Executive Function; C=Collect; CBD=cannabidiol; CGI-I=Clinical Global Impression-Improvement; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination; EQ-5D-5L=standardized measure of health status; HADS=Hospital Anxiety and Depression Scale; PedsQL=Pediatric Quality of Life Inventory; QoL=quality of life; QOLCE=Quality of Life in Childhood Epilepsy; R=Review

NOTE: If a subject has a birthday during the study that makes a previously unrequired assessment now required (eg, Tanner staging in a male subject who turns 8 years old during the study), this assessment(s) should be initiated at visits subsequent to the birthday.

**** de Novo subjects are subjects who did not participate in one of the core studies and may or may not be currently taking STP.**

a: For subjects enrolling from one of the core studies use data collected at Visit 12 and Visit 13 of Study ZX008-1501 or ZX008-1502.
For de novo subjects, a screening period up to 28 days is required. During this period, informed consent is required prior to any study-related procedures. All results to determine eligibility must be reviewed prior to receiving the first dose of study study medication at Visit 1.
For all subjects, clinical laboratory results and all ECHO/ECG results must be available and meet eligibility criteria prior to receiving the first dose of study medication at Visit 1.

b: De Novo subjects must meet entry criteria 3 to 7, and 10, including having had ≥4 convulsive seizures (tonic, tonic-atonic, tonic-clonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.

c: At the discretion of the investigator, Visit 2 may be conducted as a phone visit.

d: Or early termination.

e; Follow-up ECG, ECHO, and physical examination will be performed 3 and 6 months after study completion or early termination (see Section 6.3).

f: For subjects enrolling from one of the core studies, use core study Visit 12 information unless complete neurological examination is warranted based on significant changes in subject status.

g: ECHOs will be performed at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33.

h: The Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33 ECHO may be performed any time within 3 weeks prior to the study visit. If a subject discontinues early from the study, the ECHO should be scheduled as soon as practical (see Table 7).

i: Females of child-bearing potential

j: For subjects enrolling from one of the core studies, use data collected at Visit 12 of ZX008-1501 or ZX008-1502 for Visit 1 unless clinical laboratory evaluation is warranted based on significant changes in subject status. Visit 2 clinical laboratory evaluation is optional based on subject status for all cohorts.

k: Visits 6, 15, and 27 only.

l: Visits 3 and 4 (Months 1 and 2) only.

m: Only adverse events related to cardiac safety will be collected at this visit (see Table 7).

n: Not to be completed for de novo subjects >18 years old.

o: For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial.

Table 2. Schedule of Assessments for Subjects from Core Study ZX008-1504

Study Assessments	**OLE Treatment Period**					**Post-Dosing**	**Cardiac Follow-up**
Visit Number	**Visit 1[a]**	**Visit 2[b]**		**Visits 3-15 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33)**	**Visit 16[c] (EOS/ET) Month 36**	**Visit 17[m]**	**Visit 18, 19[m]**
Study Day	**1[a]**	**15**		**30, 60, 90, 180, 270, 365, 455, 545, 635, 725. 815, 905, 995**	**1085**	**1099**	**3 and 6 months post last dose**
		Clinic	**Phone**				
Informed Consent	X						
Entry Criteria	X						
Demographics	X						
Medical/Neurological History	X[a]						
Epilepsy History	X[a]						
Physical Examination, complete	X[a]				X		X[d]
Physical Examination, abbreviated		X		X			X[d]
Neurological Examination, complete	X[e]				X		
Neurological Examination, abbreviated		X		X			
Vital signs	X	X		X	X		
Weight, Height, BMI	X[a]	X		X	X		
12-lead ECG	X[a]			X	X		X[d]
Doppler ECHO	X[a]			X[f,g]	X		X[d]
Urine Pregnancy Test[h]	X			X	X		
Clinical laboratory evaluation (hematology/clinical chemistry/urinalysis, etc)	X[i]	X[i]		X	X		
Urine THC Panel/Whole blood CBD	X[a]			X	X		
Plasma sample for background AEDs		X		X	X		
Tanner Staging (for subjects > 7 years old)	X[a]			X[j]	X		X[j]
C-SSRS	X[a]			X	X		
CGI-I (assessed by parent/caregiver)	X[a]			X	X		
CGI-I (assessed by principal investigator)	X[a]			X	X		
QOLCE	X[a]			X	X		
EQ-5D-5L (QoL of parent/caregiver)	X[a]			X	X		
BRIEF	X[a]			X	X		
Healthcare utilization questions	X[a]			X	X		

continued

Table 2. Schedule of Assessments for Subjects from Core Study ZX008-1504 (continued)

Study Assessments	**OLE Treatment Period**					**Post-Dosing**	**Cardiac Follow-up**
Visit Number	**Visit 1[a]**	**Visit 2[b]**		**Visits 3-15 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33)**	**Visit 16[c] (EOS/ET) Month 36**	**Visit 17[m]**	**Visit 18, 19[m]**
Study Day	**1[a]**	**15**		**30, 60, 90, 180, 270, 365, 455, 545, 635, 725. 815, 905, 995**	**1085**	**1099**	**3 and 6 months post last dose**
		Clinic	**Phone**				
Karolinska Sleep Scale	X[a]			X	X		
Sleep quality/mealtime behavior questions	X[a]			X	X		
PedsQL	X[a]			X	X		
Study medication palatability assessment				X[k]			
Subject Diary	D	C/R/D	R	C/R/D	C/R	C/R	
Study Medication	D[b]	C/R/D	R	C/R/D	C/R/D	C/R	
Daily Diary Completion	---------- X ----------						
Concomitant Medications	X[a]	----------X----------					
Adverse Events	X[a]	----------X----------					
Adverse events of special interest	X[a]	----------X----------					X[l]

AED=antiepileptic drug; BMI=body mass index; BRIEF=Behavior Rating Inventory of Executive Function; C=Collect; CBD=cannabidiol; CGI-I=Clinical Global Impression-Improvement; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination; EQ-5D-5L=standardized measure of health status; HADS=Hospital Anxiety and Depression Scale; PedsQL=Pediatric Quality of Life Inventory; QoL=quality of life; QOLCE=Quality of Life in Childhood Epilepsy; R=Review

NOTE: If a subject has a birthday during the study that makes a previously unrequired assessment now required (eg, Tanner staging in a male subject who turns 8 years old during the study), this assessment(s) should be initiated at visits subsequent to the birthday.

a: For subjects from the core Study ZX008-1504 Cohort 1, use data collected at the last visit of the transition period; for subjects from core Study ZX008-1504 Cohort 2 use data collected at the Visit 12 and Visit 13.
For de novo subjects, a screening period up to 28 days is required. During this period, informed consent is required prior to any study-related procedures. All results to determine eligibility must be reviewed prior to receiving the first dose of study drug at Visit 1.
For subjects from ZX008-1504 Cohort 2 and de novo subjects, clinical laboratory, ECHO, and ECG results must be available and meet eligibility criteria prior to receiving the first dose of study drug at Visit 1.

b: At the discretion of the investigator, Visit 2 may be conducted as a phone visit.

c: Or early termination.

d: Follow-up ECG, ECHO, and physical examination will be performed 3 and 6 months after study completion or early termination (see Section 6.3).

e; Unless complete neurological examination is warranted based on significant changes in subject status, use data collected at the last visit of the transition period of Study ZX008-1504 Cohort 1 and for subjects from Study ZX008-1504 Cohort 2, use data collected at the Visit 12.

f: ECHOs will be performed at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33.

g: The Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33 ECHO may be performed any time within 3 weeks prior to the study visit. If a subject discontinues early from the study, the ECHO should be scheduled as soon as practical (see Table 7).

h: Females of child-bearing potential

i: Unless clinical laboratory evaluation is warranted based on significant changes in subject status, use data collected at the last visit of the transition period of Study ZX008-1504 Cohort 1; for subjects from Study ZX008-1504 Cohort 2, use data collected at the Visit 12. For Visit 2, clinical laboratory evaluation is optional based on subject status.

j: Visits 6, 15, and 27.

k: Visits 3 and 4 (Months 1 and 2) only.

l: Only adverse events related to cardiac safety will be collected at this visit (see Table 7).

m: For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial.

1. INTRODUCTION

1.1 BACKGROUND INFORMATION ON INDICATION STUDIED

ZX008 (fenfluramine hydrochloride) is under clinical development for the adjunctive treatment of patients with Dravet syndrome (DS) 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

Dravet syndrome, previously known as severe myoclonic epilepsy of infancy (SMEI), is a rare and severe form of epilepsy first described by Charlotte Dravet in 1978 (Dravet 1978). The International League Against Epilepsy (ILAE) considers Dravet syndrome a developmental and epileptic encephalopathy, "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).

Dravet syndrome is estimated to affect 1 out of every 15,700 live births in the US and less than 1 in 20,000 persons in the European Union (Wu 2015; EMA 2014). Dravet syndrome is responsible for 7% of the severe epilepsies starting before the age of 3 years (Ceulemans 2004).

The diagnosis of Dravet syndrome is based on clinical signs and symptoms, though the presence of a mutation in the SCN1A gene is considered a likely, though not definitive, marker for the disorder (Dravet 2011; Fujiwara 2006). Dravet syndrome is usually not diagnosed until at least 1 year of age (Cooper 2016) and is characterized by medically intractable seizures along with motor and neurodevelopmental comorbidities. Onset of the first seizure typically occurs in the first year of life (usually at 5 to 8 months of age) in otherwise healthy infants and most often consists of prolonged, unilateral or generalized, clonic seizures provoked by fever (Orphanet 2014; Ceulemans 2004; Dravet 2011). These patients will have poor response or worsening seizures to standard antiepileptic drugs, in particular, sodium channel antagonist medications (Dravet 2011).

After the first year, other types of seizures often begin to occur with high frequency and include (1) convulsive seizures consisting of generalized clonic seizures, generalized tonic-clonic (GTC) seizures or alternating unilateral clonic seizures (in the youngest patients, they often evolve into status epilepticus [SE]); (2) myoclonic seizures (appearing between the ages of 1 and 5 years); (3) atypical absences (appearing at different ages between 4 months and 6 years or later); (4) focal seizures with or without secondary generalization (appearing between the ages 4 months and 4 years); or (5) rarely, tonic seizures (TS) (Dravet 2011). Individuals with Dravet syndrome are at higher risk for SE that often results in injury and hospitalization (Ceulemans 2004). A high incidence for SUDEP (sudden expected death in epilepsy) exists in

Dravet syndrome with the major risk factor being the frequency of generalized tonic-clonic seizures (Harden 2017).

Dravet syndrome is highly treatment-resistant and affects infants, children, adolescents, and adults. In general, convulsive seizure semiology is similar in patients across ages, although seizures tend to become less frequent and less severe in patients with Dravet syndrome as they enter adulthood (Lagae 2018). Generalized convulsive seizures, mostly reported as generalized tonic-clonic seizures persist into adulthood, often with a focal onset. These seizures are less frequent than in childhood and are mostly nocturnal. Some of these major convulsive seizures may have less typical aspects, for example, bilateral or asymmetric tonic posturing, followed in some cases by a tonic vibratory state or clonic movements (Oguni, 2001; Akiyama 2009). Throughout the lives of patients with Dravet syndrome, frequent and disabling seizures are associated with significant neurobehavioral, cognitive, developmental, and motor comorbidities,

1.1.1 Existing Treatment for Dravet Syndrome

Currently no treatment algorithm exists for Dravet syndrome as recommended by the ILAE (International League Against Epilepsy) or any other similar medical entity. The main treatment goal in Dravet syndrome aims to reduce the frequency, duration, and severity of seizures with the ultimate goal of complete or near-complete seizure-freedom (Wirrell 2017). Attaining seizure-freedom or near seizure-freedom may be particularly important during the early developmental years. However, even with currently available AED polypharmacy, seizure-freedom or near seizure-freedom is rarely achieved (Dravet 2000; Dravet 2005, Dravet 2011, Chiron 2011). Commonly prescribed anticonvulsant medications, the sodium channel antagonists such as phenytoin and carbamazepine, exacerbate seizures in Dravet syndrome and are thus not useful (Wirrell 2016). Treatment for Dravet syndrome involves finding the best combination of medicines to treat seizures with tolerable side effects, preventing SE, and reducing comorbidity and mortality risk. Elimination or significant reduction of prolonged convulsive seizures and SE should represent the highest priority in treatment (Wirrell 2017).

Stiripentol and cannabidiol are the only 2 treatments approved for seizures associated with Dravet syndrome.

Other therapies, topiramate (TPM), levetiracetam (LEV), and bromide may provide efficacy as adjunctive therapy for some patients (Chiron 2011). Published uncontrolled studies with LEV (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 (IV) 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.

Due to the severe and refractory nature of seizures associated with Dravet syndrome and given the risks of premature death from SUDEP, cognitive deficits, and other neurological consequences, there remains an urgent unmet medical need for the treatment of convulsive seizures associated with Dravet syndrome. The frequent and disabling seizures of different types, and the associated significant neurobehavioral, cognitive, developmental, and motor comorbidities that characterize Dravet syndrome, have a major negative impact on the patient's quality of life, as well as on their families. The neurobehavioral, cognitive, developmental, and motor comorbidities are at least partly caused by the poor control of seizures resulting in ongoing damage to the brain (Wolff 2006; Ragona 2011; Nabbout 2013; Wirrell 2016). A high incidence for SUDEP exists in Dravet syndrome with the major risk factor being the frequency of generalized tonic-clonic GTC seizures.

Dravet syndrome drains a family emotionally, physically, and financially. Parents/caregivers suffer emotional exhaustion and anxiety related to the "fear of the next seizure" and "will this be the seizure that kills my child" (Campbell 2018). Patients with the highest seizure frequency tend to have more comorbidities and a lower quality of life (Lagae 2017). A 2006 study identified the challenges faced by parents caring for children with Dravet syndrome, reporting that the combination of persistent, severe seizures, together with developmental, behavioral, and sleep issues result in a high caregiver stress load with little ability to find respite and relief (Nolan 2006). The comorbid conditions, high mortality, disorder management requirements, and difficulties with family adaptation result in constant distress (Skluzacek 2011). In addition, Dravet syndrome is associated with extensive healthcare costs due to increased medical care use and intensive caregiver supervision as well as indirect burdens such as losses of productivity, family time, and leisure (Whittington 2018). The unremitting seizure episodes account for a high degree of healthcare resource utilization including hospitalizations, emergency room visits, and emergency transport services (Strzelczyk 2014). Aras and coworkers report 4 or more emergency room admissions in > 10% of children and up to 30 admissions per year for some (Aras 2015). The impacts of Dravet syndrome typically not considered by healthcare professionals when making treatment decisions include the child's expressive and receptive communications with family members, disruption of daily activities, and caregivers' social interactions (Villas 2017; Nabbout 2013).

A more effective treatment for Dravet syndrome that will abolish or significantly reduce seizure activity in a higher proportion of patients and provide periods of seizure freedom is urgently needed. Moreover, such outcomes could also lessen chronic brain injury and neuroinflammation due to unremitting seizures and thus potentially also improve Dravet syndromes' associated comorbidities.

1.2 BACKGROUND INFORMATION ON STUDY PRODUCT

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

Fenfluramine was introduced in the USA in 1973. Products containing fenfluramine and D-fenfluramine were withdrawn from the USA market in 1997 after reports of heart valve disease and pulmonary hypertension (Connolly 1997; CDC 1997; Wong 1998). While the risk/benefit relationship for fenfluramine is thus considered unfavorable for the treatment of obesity in adults, establishing seizure control in DS or any of the catastrophic childhood epilepsies might lead to a more acceptable risk/benefit profile for fenfluramine, especially if lower doses can be used successfully.

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 IB). There is also a large body of information concerning its clinical safety profile.

1.3 CLINICAL DATA

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.

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 [redacted] who was discontinued from the study; SAEs of seizure leading to hospitalization, drowsiness, reduced appetite, and weight loss in a [redacted] 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 [redacted] in the placebo group; lethargy in a [redacted] 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 for more detailed information on the safety and efficacy of ZX008.

1.4 PRECLINICAL DATA

The pharmacokinetics (PK) of fenfluramine, norfenfluramine and their respective isomers has 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. 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 preclinical data on ZX008 are available in the Investigator's Brochure (ZX008 IB).

1.5 PHARMACOKINETICS

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.

Study 1 and Study 1504 Cohort 2

Pharmacokinetic parameters of fenfluramine and norfenfluramine for patients with Dravet syndrome were determined using a population pharmacokinetic (PopPK) model developed using PK data from both healthy volunteers and patients with Dravet syndrome and are provided in the Table 3 below.

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

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

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

Study 1504 Cohort 2 required STP as a concomitant medication. Although the dose of ZX008 in Study 1504 Cohort 2 was lower than the high dose in Study 1, fenfluramine AUC_{0-24} values were approximately 130% higher in Study 1504 Cohort 2, than the high dose in Study 1, and norfenfluramine AUC_{0-24} values were approximately 60% lower than in Study 1. However, the clinical results indicated that the efficacy and AE profile were similar between Study 1 and Study 1504, indicating that the dose adjustment studied for the concomitant use of the STP regimen met the intended clinical outcome.

1.6 CLINICAL PHARMACOLOGY

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

- Coadministration of ZX008 with the STP regimen (STP with CLB and/or VPA) resulted in an increased fenfluramine and decreased norfenfluramine concentrations, and therefore a dose adjustment is used in the clinical trials.

- STP is the predominant perpetrator of the interaction; while VPA and CLB do not have a significant independent impact on the PK of fenfluramine or norfenfluramine, whether administered with or without STP.

- Coadministration of ZX008 with CBD at steady state resulted in increased fenfluramine concentrations but this increase was within the range of [redacted] 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.

1.7 BACKGROUND INFORMATION ON REFERENCE PRODUCT

Not applicable.

1.8 RATIONALE FOR CURRENT STUDY

The rationale for conducting this open-label extension study is primarily to evaluate the long-term safety of ZX008 in DS. This protocol also provides the opportunity for continued treatment for subjects responding to treatment from the Phase 3 double-blind studies, and an opportunity for initial treatment with ZX008 for subjects randomized to placebo in those studies.

1.9 RATIONALE FOR INCLUDING DE NOVO SUBJECTS

Subjects who are >18 to ≤35 years of age at the time of screening, and who meet all other eligibility criteria may be eligible for participation after discussion with the Medical Monitor and sponsor about the potential risks and benefits for receiving ZX008. Participation for these subjects will be at the discretion of the sponsor.

Epileptic seizures tend to become less frequent and less severe after childhood; however, the mortality rate remains high. One study on the long-term outcome of 24 adult patients with DS reported 5 (20.8%) deaths, at a mean age of 24.8 years, one by status epilepticus, three by sudden unexpected death in epilepsy (SUDEP), and one of unknown cause (Genton 2011). Fever sensitivity (temperature variations) persists throughout the clinical course of DS, but its impact on seizure frequency and severity is milder than in infancy. Generalized convulsive seizures, mostly reported as generalized tonic-clonic seizures persist, often with a focal onset but are less frequent than in childhood and mostly nocturnal. Some of these major convulsive seizures have less typical aspects, for example, bilateral or asymmetric tonic posturing, followed in some cases by a tonic vibratory state or clonic movements (Oguni 2001;

Akiyama 2010). Other seizures like myoclonic seizures, atypical absences, and complex partial seizures are less common in adulthood. Motor abnormalities are also common in adulthood, as is intellectual disability. Dependency in adulthood is nearly constant.

Including subjects >18 to ≤35 years of age provides the opportunity to investigate the impact of ZX008 on DS outcomes as subjects transition to adulthood.

1.10 RISK-BENEFIT ASSESSMENT

Fenfluramine has been used successfully for up to 30 years in Belgium in refractory pediatric epilepsy patients, including those with DS (Boel 1996, Ceulemans 2012, Ceulemans 2016, Schoonjans 2016, Schoonjans 2017). The efficacy and safety of this therapeutic approach has been reported to be overwhelmingly favorable. Of the 15 DS treated patients, 10 (67%) were reported as seizure-free, with the average time of seizure-freedom being 6 years (range 1-19 years). Twelve patients (87%) had a greater than 90% reduction in seizure frequency and 14 patients (93%) with greater than 70% reduction in seizure frequency. No patients experienced emergence of clinical valvulopathy or pulmonary hypertension. The doses tested thus far in DS range from 0.12 to 0.9 mg/kg/day in subjects over 1 year of age to adults. Fenfluramine has also been administered to over 500 children with neurobehavioral conditions, including autism and ADHD with good safety and tolerability. Doses tested in these pediatric studies ranged from 0.65 mg/kg/day to 3.6 mg/kg/day, but a commonly used dose was 1.5 mg/kg/day. Occasionally, fixed doses of 30 to 80 mg were used.

In addition, ZX008 demonstrated a statistically significant and clinically meaningful reduction in monthly convulsive seizure frequency in Study 1 and Study 1504 Cohort 2 and was generally well tolerated. There was no clinical or echocardiographic evidence of cardiac valvulopathy or pulmonary hypertension and no patient discontinued participation or required a change in monitoring in the study due to cardiac factors. The PK exposure associated with the doses of ZX008 in the DS studies of 0.2 mg/kg/day to 0.8 mg/kg/day administered orally [in equally divided doses twice per day (BID)] is expected to be lower than that obtained at the doses used in the past for the treatment of obesity in adults and of neurobehavioral conditions in children and adolescents (ZX008 IB). The doses used in this study are based on the data from the DS patients being successfully treated in Belgium discussed above and supported by results from Study 1 and Study 1504 Cohort 2.

Interim results from this open-label study show that the effects observed during the double-blind studies were durable and long-lasting; the reduction in convulsive seizures for subjects in Study 1503 was maintained throughout study participation of up to 3 years at the time of the interim analysis, with no evidence for developing tolerance. The pharmacologic and toxicological profile for the active pharmaceutical ingredient, fenfluramine, following oral administration is well established (ZX008 IB).

The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and should detect expected and unexpected treatment-emergent adverse events. Subjects will be enrolled into this study from the core studies where they had been transitioned to the lowest dose of ZX008 (0.2 mg/kg/day; maximum 30 mg/day or 20 mg/day for subjects from ZX008-1504 Cohort 1 dose regimen 3 or Cohort 2) and will remain on this dose for the first month of this study. After this time, the dose of ZX008 may be adjusted based on effectiveness and tolerability. For subjects that participated in core studies ZX008-1501, ZX008-1502, and dose regimen 1 or 2 from Cohort 1 of ZX008-1504 dose increases may be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day (maximum dose 30 mg/day), and these increases should not occur earlier than every 14 days at each dose level. For subjects that participated in core study ZX008-1504 Cohort 1 dose regimen 3 and Cohort 2 and 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 may only occur after a review of the diary and reported adverse events (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 situation. Dose adjustments outside of these parameters must be discussed with the Medical Monitor prior to initiation.

It is acknowledged that the initial dose of ZX008 in this study, 0.2 mg/kg/day, may or may not be effective or may be less effective than 0.8 mg/kg/day (or 0.5 mg/kg/day for subjects taking concomitant STP) for some subjects and some subjects may experience a worsening of their seizure condition after transitioning to the lower dose. However, there is benefit in identifying a minimally effective dose for all subjects in the study since the cardiotoxicity of fenfluramine appears to be dose-related in adults. The dosing instructions of this protocol permit dose adjustment during the first month of fixed dosing at 0.2 mg/kg/day if a clinically meaningful worsening occurs, such as an increase in frequency, severity or duration of existing seizures, or emergence of a new seizure type.

The approximate volume of blood (240 mL) planned for collection from each subject over the course of the entire study (approximately 3 years, but not including repeat or additional tests ordered by the investigator) presents no undue risk to the subjects.

The ZX008 0.2 mg/kg/day, 0.4 mg/kg/day, 0.6 mg/kg/day, 0.8 mg/kg/day, and 0.5 mg/kg/day (in subjects taking concomitant STP) doses are believed to be therapeutic doses, which could provide sufficient anti-epileptic support for a sustained period of time during the study.

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

The primary objective of the study is:

- To assess the long-term safety and tolerability of ZX008.

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To assess the effect of ZX008 relative to the pre-ZX008 baseline on the following effectiveness measures:
  - The change in the frequency of convulsive seizures from Visit 3 to Visit 8 (ie, Day 31 to Day 365) and for the entire Year 1 treatment period (ie, Visit 1/Day 1 to Visit 8/ Day 365)
  - The proportion of subjects who achieve a ≥ 40%, ≥ 50%, and ≥ 75% reduction in convulsive seizure frequency
  - The longest convulsive seizure-free interval
  - The percentage of convulsive seizure-free days
  - The non-convulsive seizure frequency
  - The convulsive + non-convulsive seizure frequency
- To estimate the incidence of the following on subjects receiving ZX008:
  - Use of rescue medication
  - Hospitalization to treat seizures
  - Status epilepticus (SE)
- To assess the effect of ZX008 relative to the pre-ZX008 baseline on the following QoL measures:
  - Quality of Life in Childhood Epilepsy (QOLCE) score
  - Pediatric Quality of Life Inventory™ (PedsQL score)
  - PedsQL Family Impact module score
  - QoL of the parent/caregiver using the standardized measure of health status (EQ-5D-5L scale
  - Affective symptoms of the parent/caregiver using the Hospital Anxiety and Depression Scale (HADS)
- To assess the effect of ZX008 on the following QoL measures:
  - Clinical Global Impression – Improvement (CGI-I) rating, as assessed by the principal investigator
  - CGI-I rating, as assessed by the parent/caregiver

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for subjects who participated in core study ZX008-1504 are:

- To assess the effect of ZX008 on the following QoL measures:
  - Sleep quality and mealtime behavior, as assessed by the parent/caregiver
  - Karolinska Sleep Scale
  - Health and social care resource use (These measures include planned and unplanned hospital visits, use of ambulances, General Practitioner (GP) visits, speech and language therapy utilization, occupational and physical therapy utilization)

2.4 STUDY ENDPOINTS

2.4.1 Effectiveness Endpoints

The effectiveness endpoints of the study are:

- Number of seizures by type
- Convulsive seizure-free interval
- CGI-I as assessed by parent/caregiver
- CGI-I as assessed by principal investigator
- QOLCE to measure changes in quality of life of the subject
- PedsQL to measure changes in quality of life of the subject
- PedsQL Family Impact module to measure changes in quality of life of the parent/caregiver
- QoL of parent/caregiver using the EQ-5D-5L scale
- Affective symptoms of parent/caregiver using the HADS (in parents/caregivers from core studies ZX008-1501 and ZX008-1502 only)
- Duration of prolonged seizures (seizure type that, during pre-Z008 baseline, had duration > 2 minutes)
- Number of episodes of SE
- Number of instances of rescue medication use and number of doses
- Number of inpatient hospital admissions due to seizures

2.4.2 Safety Endpoints

The safety endpoints of the study are:

- AEs
- Laboratory safety (hematology, chemistry, urinalysis)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Physical examination
- Neurological examination

- 12-lead electrocardiogram (ECGs)
- Doppler echocardiogram (ECHOs)
- Body weight
- Behavior Rating Inventory for Executive Function (BRIEF) to measure cognition

2.4.3 Exploratory Endpoints

For subjects who participated in core study ZX008-1504 only, the exploratory endpoints of this study are:

- Health and social care resource use, including GP visits, speech and language, occupational and physical therapy, in addition to acute hospital and institutional length of stay, loss of work, etc.
- Sleep quality
- Mealtime behavior
- Karolinska Sleepiness Scale to measure the effect of study medication on sleepiness

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This is an international, multicenter, open-label, long-term safety study of ZX008 in pediatric and young adult subjects with DS. Subjects eligible for participation are those who have successfully completed 14 weeks of treatment in core studies ZX008-1501 or ZX008-1502, and 15 weeks of treatment in core study ZX008-1504 Cohort 2, or successfully completed core study ZX008-1504 Cohort 1, and are candidates for continuous treatment for an extended period of time. In addition, subjects who are >18 to ≤35 years of age at the time of screening, and who meet all other eligibility criteria may be eligible for participation after discussion with the Medical Monitor and sponsor about the potential risks and benefits for receiving ZX008. Participation for these subjects will be at the discretion of the sponsor.

This trial will consist of an up to 36-month open-label extension (OLE) Treatment Period and a 2-week Post-Dosing Period. Thus, subjects who complete this trial will have been treated with ZX008 for a minimum of up to 3 years (including their participation in both the core study and this study). Subjects who did not participate in one of the core studies will undergo a screening period up to 28 days to confirm eligibility prior to receiving their first dose in the OLE Treatment Period

During the OLE Treatment Period, all subjects will be treated initially with 0.2 mg/kg/day for 1 month to assess effectiveness of this dose in all study subjects. After 1 month at a dose of 0.2 mg/kg/day, the investigator may adjust the dose of each subject based on effectiveness and tolerability. For subjects who are not receiving concomitant STP, including de novo subjects and those who participated in core studies ZX008-1501, ZX008-1502, and dose regimen 1 or 2 from Cohort 1 of ZX008-1504, dose changes should be made in increments of 0.2 mg/kg/day, to a maximum of 0.8 mg/kg/day but not to exceed total dose of 30 mg/day. For subjects who are receiving concomitant STP, including de novo subjects and those who participated in core study ZX008-1504 Cohort 1 dose regimen 3 and Cohort 2, and 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 should not occur earlier than every 14 days at each dose level. Dose increases may only occur after a review of the diary and reported AEs, and if, in the investigator's opinion, seizure frequency, severity, and/or duration indicates a change in medication regimen is warranted. Dose decreases for tolerability can occur at the investigator's discretion, in dose amounts and frequency appropriate for the situation. ZX008 dose adjustments outside of these parameters should be discussed with the Medical Monitor prior to initiation.

In addition, if a subject has been stable on the same dose of ZX008 for 6 months or longer, investigators may adjust the doses of one or more of the other concomitant AEDs as per typical clinical practice. Concomitant AEDs may be withdrawn completely but all subjects must remain on a minimum of 1 concomitant AED plus ZX008. No new concomitant AEDs or

antiepileptic treatments may be introduced while in this study. All medication dose changes must be documented with a clinical explanation and justification. Concomitant AED dose adjustments outside of these parameters should be discussed with the Medical Monitor prior to initiation.

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

A follow-up ECG and ECHO will be performed 3 and 6 months after study drug discontinuation for early termination and for those subjects who complete the study.

Caregivers will use a diary daily to record the number/type of seizures, dosing, and use of rescue medication. A schedule of assessments is provided in Table 1 and Table 2.

After at least 1 year of treatment in Study 1503 subjects who participated in one of the core studies will transition to a separate extension study (Study 1900) once that study is approved and the study site is initiated. Continuation in a separate extension protocol will be based on benefit/risk and continued eligibility criteria being met. De novo subjects must have participated in this trial for at least 3 months with at least 1 ECHO completed and continue to meet eligibility requirements to be eligible to transition to a separate extension protocol. Alternatively, subjects will transition to commercial product once it is available. For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial. Subjects who transition to commercially available drug must have an ECHO within 3-6 months before starting commercial drug and will have follow-up ECHOs within the required timeframe while on commercial drug.

3.2 NUMBER OF SUBJECTS

Up to approximately 340 subjects from the core studies and up to 50 subjects who did not participate in the core studies may be enrolled.

3.3 STUDY DURATION

The duration of participation in the study for an individual subject is expected to be up to 158 weeks, plus follow-up safety visit 3 and 6 months after the last dose:

- OLE Treatment Period - 36 months (156 weeks)
- Post-Dosing Visit - 2 weeks after study completion or early termination
- Cardiac Follow-up (ECG and ECHO) - 3 and 6 months after study drug discontinuation for early termination and for those subjects who complete the study; not applicable to subjects who transition to commercial product.

3.4 NUMBER OF STUDY CENTERS

The study expects to use up to approximately 75 research centers in North America, Europe, Australia and Japan.

3.5 RATIONALE FOR STUDY DESIGN AND CHOICE OF TREATMENT GROUPS

It is recognized that performing clinical studies in young children or in subjects with reduced cognitive capacity presents particular practical and ethical issues. However, given the seriousness of DS, and the possible consequences of current inadequate treatments, the use of children with DS in this study is considered justified. The study design has incorporated an initial 1-month of treatment at the lowest dose (ZX008 0.2 mg/kg/day) after which time the investigator may adjust the dose based on effectiveness and tolerability. After the first month, dose increases will be made incrementally every 14 days to ensure adequate time to acclimate to the new dose. Dose decreases for tolerability can occur at the investigator's discretion, in dose amounts and frequency appropriate for the situation. The duration of the study, up to 36 months, will allow for collection of appropriate data to characterize the safety profile of ZX008.

3.6 PREMATURE TERMINATION OF STUDY

The Sponsor can terminate the study prematurely at any time for medical or ethical reasons at individual study sites or at all study sites. The investigator will be notified in writing, outlining

the reasons for the termination. Instructions will be provided if assessments beyond those described in the study protocol need to be conducted.

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 6.1.5 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

3.7.2 International Pediatric Cardiac Advisory Board (IPCAB)

The International Pediatric Cardiac Advisory Board (IPCAB) is an advisory body to the Sponsor that monitors cardiac safety of the ZX008 clinical trials and provides advice to the IDSMC. The IPCAB charter outlines the roles and responsibilities of the committee and guide its operations, and review of individual subject cases. The IPCAB consists of individuals external to the Sponsor who have relevant experience in cardiology, pediatric cardiology, and echocardiography. The IPCAB 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.

All ECHO examinations performed throughout the trial will be sent to an experienced pediatric cardiologist central reader (Biomedical Systems, Inc.). If the central reader classifies a subject as having met a pre-defined threshold value indicative of potential cardiac valvulopathy or pulmonary hypertension, or any other unexpected cardiac adverse event, the case will then be sent for secondary adjudication by one or more members of the IPCAB according to the procedures outlined in the IPCAB manual. In addition, member of the IPCAB will perform audits of ECHOs deemed normal by the central cardiac reader.

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 aged 2 to 18 years inclusive, as of the day of the core study Screening Visit.
2. Subject has satisfactorily completed the core study in the opinion of the investigator and the Sponsor.
   NOTE: Those subjects who do not complete the 12-week Maintenance Period of the core study may, on a case-by-case basis, be eligible for entrance after consideration of the circumstances of the early termination and the potential benefit-risk of continued participation in a ZX008 trial. The decision whether to permit open-label extension study participation resides solely with the Sponsor, who may consult with the site investigator, the IPCAB and/or the IDSMC.
3. Subject is male or non-pregnant, non-lactating female. Female subjects of childbearing potential must not be pregnant or breast-feeding. Female subjects of childbearing potential must have a negative urine pregnancy test. 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 documented medical history to support a clinical diagnosis of DS, where convulsive seizures are not completely controlled by current antiepileptic drugs.
5. Subject has been informed of the nature of the study and informed consent has been obtained from the legally responsible parent/guardian.
6. Subject has provided assent in accordance with IRB/IEC requirements, if capable.
7. Subject's caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.
8. Subject's parent/caregiver has been compliant with diary completion during the core study, in the opinion of the investigator (eg, at least 90% compliant).
9. Subjects entering from study ZX008-1504 must be receiving a therapeutically relevant and stable dose of CLB and/or VPA, and STP (Cohort 1 dose regimen 3 and Cohort 2 only) for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
10. Subjects who are >18 to ≤35 years of age at the time of screening and did not participate in one of the core studies must meet criteria 3 to 7 above and the following criteria below in order to be considered for participation. Participation is at the discretion of the Sponsor:
    a. Onset of seizures in the first year of life in an otherwise healthy infant.

b. A history of seizures that are either generalized tonic-clonic or unilateral clonic or bilateral clonic, and are prolonged.
c. Initial development is normal.
d. History of normal brain MRI without cortical brain malformation.
e. Lack of alternative diagnosis.
f. Meets one of the following 3 confirmatory diagnostic criteria:
    i. Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal has developed after the first seizure type.
    ii. Prolonged exposure to warm temperatures induces seizures and/or seizures are associated with fevers due to illness or vaccines, hot baths, high levels of activity and sudden temperature changes and/or seizures are induced by strong natural and/or fluorescent lighting, as well as certain visual patterns.
    iii. Genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis.)
g. Subject has been approved for study inclusion by the Epilepsy Study Consortium.
h. Subject does not have an exclusionary cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination and is approved for entry by the central cardiac reader. Exclusionary abnormalities include, but are not limited to:
    i. Mild or greater mitral or aortic valve regurgitation in subjects >18 yrs of age
    ii. Possible signs of pulmonary hypertension with abnormal or greater than upper limit of normal values
    iii. Evidence of diastolic dysfunction
i. Subject must have had ≥4 convulsive seizures (tonic, tonic-atonic, tonic-clonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.
j. All medications or interventions for epilepsy (including ketogenic diet [KD] and vagal nerve stimulation [VNS]) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study.
11. Subject's parent/caregiver is willing and able to be compliant with diary completion, 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 or past history of cardiovascular or cerebrovascular disease, myocardial infarction or stroke.
3. Subject from one of the core studies with current cardiac valvulopathy or pulmonary hypertension that the investigator, parent, IPCAB, IDSMC, or Sponsor deems clinically significant and warrants discontinuation of study medication.
4. For de novo subjects: possible signs of pulmonary hypertension with abnormal or greater than upper limit of normal values
5. Subject has current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month.
6. 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.
7. Subject has a current or past history of glaucoma.
8. Subject has moderate or severe hepatic impairment. Asymptomatic subjects with mild hepatic impairment (elevated liver enzymes < 3x upper limited of normal [ULN] and/or elevated bilirubin < 2x ULN) may be entered into the study after review and approval by the Medical Monitor in conjunction with the Sponsor, in consideration of comorbidities and concomitant medications.
9. Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin reuptake inhibition; atomoxetine, or other centrally-acting noradrenergic agonist; cyproheptadine, and/or cytochrome P450 (CYP) 2D6/3A4/2B6 inhibitors/substrates (Appendix 1). (Note: Short-term medication requirements will be handled on a per case basis by the Medical Monitor.)
10. Subject is currently taking carbamazepine, oxcarbazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy.
11. For subjects entering from core studies ZX008-1501, ZX008-1502, or ZX008-1504 (Cohort 1/dose regimens 1 &2): Subject is currently receiving or has received STP in the past 21 days prior to core study Visit 1.

12. Subject is unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges, and their juices beginning with Visit 1 and throughout the study.
13. Subject has positive result on urine tetrahydrocannabinol (THC) Panel or whole blood cannabidiol (CBD) at Visit 1.
14. Subject is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
15. Subject has a clinically significant condition, or has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to 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.
16. Subject has participated in another clinical trial within the past 30 days (ie, the last visit of the previous study was in the past 30 days), with the exception of the core studies.

4.3 SUBJECTS OF REPRODUCTIVE POTENTIAL

Male subjects who are sexually active with a partner of child-bearing 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 child-bearing 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. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

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

The following methods are acceptable:

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

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

4.3.1 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, if deemed appropriate by the Sponsor or investigator:

1. Development of signs or symptoms indicative of cardiac valvulopathy or regurgitation (mitral, aortic, tricuspid, pulmonary valves), or pulmonary hypertension for which IDSMC, in consultation with the IPCAB, 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.

3. Subject requires or starts using the use of an unacceptable or contraindicated 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. Subject is noncompliant with procedures set forth in the protocol in an ongoing or repeated manner.

6. Subject experiences an AE that warrants withdrawal from the clinical investigation.

7. Clinically significant worsening of seizures, judged by investigator or subject/caregiver such that treatment outside of the protocol and other than ZX008 is assumed to be in the subject's best interest. Frequent or increased use of rescue medication may be considered indicative of worsening.

8. An "actual suicide attempt" as classified by the C-SSRS.

9. It is the investigator's opinion that it is not in the subject's best interest to continue in the study.

10. Subject is found to be pregnant while on study.

Discontinuation decisions will be made at each participating site by the site investigator, except that discontinuations due to development of cardiovascular or cardiopulmonary complications are to be made by the IDMSC with input from the IPCAB and the investigator.

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

Subjects 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. The IDSMC will review the data for the development of heart valve disease and pulmonary hypertension as they occur on a case-by-case basis and at regular meetings.

In the event that the study is terminated prematurely then the procedure for termination should be followed as described in Section 3.6. Concern for the interests of the subject will always prevail over the interests of the study.

The reason for, and date of discontinuation from participation in the study must be recorded in detail in the CRF and in the subject's medical records (eg, AEs, lack of compliance, lost to follow-up, etc). If possible, the subject/subject's legal 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 6.1.5 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 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 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 4).

Table 4. 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 safe. 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.

Doses to be studied include 0.2 mg/kg/day, 0.4 mg/kg/day, 0.6 mg/kg/day, and 0.8 mg/kg/day divided into two daily doses, up to a maximum of 30 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 DESCRIPTION OF REFERENCE TREATMENT, COMPARATOR, AND/OR PLACEBO

No comparators, reference treatments, or placebo will be used in this study.

5.3 IMP ACCOUNTABILITY

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

Assignment of ZX008 bottles to the subject will be handled through an interactive voice response (IVR) or Interactive Web Response (IWR) platform. The investigator or delegate will be required to register the subject through IVR/IWR and all study medication will be assigned to the subject through the IVR/IWR. The IVR/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. At the end of the study, the dated and signed (by the investigator or delegate, eg, pharmacist) original drug accountability form must be retained at the study site as verification of final drug accountability.

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

5.4 TREATMENT ADMINISTRATION

5.4.1 OLE 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 food. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given. Administration of the initial IMP will be based on the 0.2 mg/kg/day (maximum 30 mg/day or

20 mg/day for subjects taking concomitant STP) dose and subject's weight at Visit 1 (Study Day 1). At Visits 5 to 15 (Months 3 to 33), if the subject's weight has changed ± 25% of the weight from the previous dose calculation, the IMP dose will be recalculated. Subjects will be dosed using the oral dosing syringe provided.

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

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

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

5.4.2 Taper Period

All subjects (those who complete the OLE Treatment Period or those who discontinue from the study early and are not transitioning to another ZX008 extension study or treatment with commercial drug) will be tapered off of study medication.

5.4.2.1 Taper Period for Subjects not Receiving Concomitant STP

The tapering scheme is a 2-step process for subjects who are not receiving concomitant STP, including subjects from core studies ZX008-1501 and ZX008-1502, and from study ZX008-1504 Cohort 1/Regimens 1&2. This is described in Table 5.

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

Table 5. Taper Algorithm for Subjects from Core Studies ZX008-1501, ZX008-1502, and ZX008-1504 Cohort 1/Regimens 1&2Not Receiving Concomitant STP

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 0.6 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.		

5.4.2.2 Taper Period for Subjects from Core Study ZX008-1504 Cohort 1 Regimen 3 and Cohort 2 Receiving Concomitant STP

The tapering scheme is a 3-step process for subjects receiving concomitant STP, including subjects from core study ZX008-1504 Cohort 1 Regimen 3 and Cohort 2, and is described in Table 6.

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

Table 6. Taper Algorithm for Subjects Receiving Concomitant STP

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	Taper Step 3 Days 9-14 after study completion or early termination
ZX008 0.2 mg/kg/day	Not applicable	Not applicable	Not applicable
ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day	Not applicable	Not applicable
ZX008 0.5 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day	Not applicable
Note: maximum daily dose of ZX008 is 20 mg.			

5.5 BLINDING

This is an open-label study.

5.6 PRIOR AND CONCOMITANT MEDICATION

All prior and concomitant medication will be collected in the CRF.

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

Subjects are required to take at least one concomitant AED throughout the study. During at least the first 6 months of the study, subjects will continue to receive their existing AEDs at the same dose as prior to initiating this study. However, once the subject has been stable on a ZX008 dose for at least 6 months with good seizure control, investigators will be allowed as per typical clinical practice to alter one or more other concomitant AED doses as deemed clinically appropriate. Concomitant AEDs may be withdrawn completely but all subjects must remain on a minimum of 1 concomitant AED plus ZX008. No new concomitant AEDs may be introduced while in this study. All medication dose changes must be documented with a clinical explanation and justification. Concomitant AED dose adjustments outside of these parameters should be discussed with the Medical Monitor prior to initiation.

Non-study medications and therapies that are considered necessary for the subject's welfare and will not interfere with the response to the study medication may be given at the discretion of the investigator, informing the Medical Monitor as soon as possible.

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

5.6.1 Vagal Nerve Stimulation

Subjects receiving treatment with vagal nerve stimulation (VNS) may be included as long as the VNS has been in place for at least 6 months prior to entry into the core study, or for de novo subjects prior to first dose in the OLE, and stimulation parameters have been kept constant for 4 weeks prior to core study Visit 1. During at least the first 6 months of the study, VNS stimulation parameters will be kept constant. However, once the subject has been stable on a ZX008 dose for at least 6 months with good seizure control, investigators will be allowed as per typical clinical practice to alter VNS stimulation parameters as deemed clinically appropriate. All VNS stimulation parameter changes must be documented with a clinical explanation and justification. VNS stimulation parameter adjustments outside of these boundaries should be discussed with the Medical Monitor prior to initiation. The subject's use of VNS will be recorded in the CRF.

5.6.2 Ketogenic Diet

Adherence to the KD, or a modified version of KD, is permitted during the study if the dietary habits were initiated more than 4 weeks prior to entry into the core study, or for de novo subjects 4 weeks prior to first dose in the OLE. During at least the first 6 months of the study, the KD will be adhered to. However, once the subject has been stable on a ZX008 dose for at least 6 months with good seizure control, investigators will be allowed as per typical clinical practice to alter the KD as deemed clinically appropriate. All KD changes must be documented with a clinical explanation and justification. KD adjustments outside of these parameters should be discussed with the Medical Monitor prior to initiation. The subject's use of KD will be recorded in the CRF.

5.6.3 Rescue Medication for Seizures

The subject's usual or prescribed regimen and frequency of rescue therapy for seizures should be entered into the prior and/or concomitant medication sections of the CRF.

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

5.6.4 Prohibited Concomitant Medication and Food

Alcohol in all forms (wine, beer, liquors) and amounts is prohibited during the study. The following concomitant medications/foods are prohibited during the clinical trial:

- AEDs: Phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine, retigabine/ezogabine

- STP: Subjects who are not receiving concomitant STP, including de novo subjects and those from core studies ZX008-1501, ZX008-1502, and ZX008-1504 Cohort 1/Dose Regimens 1&2 only, must be off STP for a minimum of 21 days prior to the core study or OLE Screening visit.

- Felbamate is prohibited as a concomitant medication unless the subject has been on felbamate for at least 18 months prior to the core study or OLE Screening visit, has stable liver function and hematology laboratory tests, and the dose is expected to remain constant throughout the study.

- Drugs that interact with central serotonin: imipramine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, vortioxetine

- Drugs that increase cardiovascular risk: atomoxetine

- Drugs intended to facilitate weight loss

- Other: any form of marijuana, THC and derivatives (including Epidiolex®)

- Drugs/foods that potentially interact with ZX008 via the CYP2D6, CYP3A4, and/or CYP2B6 pathways: A list of medications/foods that are to be avoided 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) is provided in Appendix 1. If medical necessity requires short-term use of one or more of these medications during the course of the study, please contact the Medical Monitor for approval.

5.7 TREATMENT COMPLIANCE

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

6. VISIT SCHEDULE

Study procedures will be conducted according to the Schedule of Assessments in Table 1 and Table 2. Time windows for all assessments are detailed in Table 7. For details on alternative procedures and allowances regarding study conduct during COVD-19 refer to Appendix 11.

Table 7. Time Windows for Assessments

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Clinic; Study Day 1)	Not applicable (this is the same visit as Visit 13 from the core study)
Visits 2 (Clinic/Phone; Study Day 15)	± 3 days
Visits 3-15 (Clinic: Study Days 30, 60, 90, 180, 270, 365, 455, 545, 635, 725, 815, 905, 995)	± 4 days
Visit 16 (Clinic; Study Day 1085)	± 4 days
Visit 17 (Clinic; Study Day 1099; post dosing)	± 4 days
Visit 18, 19 (ECHO clinic; 3 and 6 months after last dose)	+ 30 days
Blood collection for AED concentration	Prior to morning dose of AED medication

AED=antiepileptic drug (s); ECHO=echocardiogram

6.1 OLE 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, including collection of HADs, EQ-5D-5L, and PedQL Family Impact Module ratings of parent/caregiver symptoms and quality of life, must be obtained before a subject can start any of the Visit 1 procedures.

The procedure(s) for obtaining written informed consent and assent of minor (if the subject is capable of providing assent) are described in Section 11.2. For subjects from the core studies it is assumed that consent for this study will have been obtained prior to completion of procedures at

- ZX008-1501 and ZX008-1502 Visit 12/End of Study
- The last visit of the transition period of ZX008-1504 Cohort 1
- ZX008-1504 Cohort 2 Visit 12/End of Study

For de novo subjects, consent for this study must be obtained prior to any study-related procedures.

Only eligible subjects as specified by the inclusion and exclusion criteria who have successfully completed the core study, or who are >18 to ≤35 years of age at the time of screening and who meet all other eligibility criteria, will be enrolled into study ZX008-1503.

6.1.1 Screening Visit for de novo Subjects

For de novo subjects a screening period up to 28 days is required to determine eligibility prior to dosing. Clinical laboratory results and all ECHO/ECG results must be available and meet eligibility criteria prior to receiving the first dose of study medication at Visit 1. The following procedures will be performed during this screening period for all de novo subjects before the first dose of study medication:

- Obtain written informed consent for the study
- Obtain written informed consent from parent/caregiver to collect PedsQL Family Impact, HADS, and EQ-5D-5L ratings of parent/caregiver symptoms and quality of life
- Review inclusion and exclusion criteria
- Record demographic information
- Record medical, neurological, and epilepsy history
- Record current epilepsy status (number/type/duration seizures per month)
- Collect past 3 months (or available duration) of parent/caregiver seizure diary data if available (screen shots of cell phones are acceptable, as are photocopies of paper diaries or print outs) and place in source file
- Record prior medications
- Complete physical examination, including height, weight, and calculation of BMI
- Complete neurological examination
- 12-lead electrocardiogram
- Doppler ECHO (this must be obtained and results provided prior to starting ZX008)
- Vital signs
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry, hematology, urinalysis, etc)
- Urine THC panel
- Whole blood CBD
- Obtain blood sample for epilepsy genotype panel
- C-SSRS Baseline/Screening Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- Affective symptoms of parent/caregiver using the HADS scale (Appendix 8)
- Instruct parent/caregiver on use of diary

- Dispense diary (after above procedures have been concluded)
- Record AEs

Review inclusion/exclusion criteria, including echocardiogram, ECG, clinical laboratory results, and approval from the Epilepsy Study Consortium. Only eligible subjects as specified by the inclusion and exclusion criteria with an independently confirmed diagnosis of DS by the Epilepsy Study Consortium, and approved by the sponsor, will be enrolled into the study and receive 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.

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

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

1. Subjects who are found to be on a prohibited medication at the screening visit may be weaned off of that medication provided:
    a. Decisions to withdraw a disallowed concomitant medication must be made with the agreement of the prescribing physician
    b. If the medication has antiepileptic properties, a wash out of at least 5 half-lives must be completed before collection of baseline seizure data.

If a decision has been made to wean off of a medication without antiepileptic properties and the wash-out period (at least 5 half-lives) is expected to be shorter than 5 weeks, then the subject may remain in screening and chart seizures using the seizure diary.

6.1.2 Clinic Visit 1 (Study Day 1; Transition from Core Study)

6.1.2.1 Clinic Visit 1 for Subjects from Core Studies ZX008-1501 or ZX008-1502

The following procedures will be performed during Visit 1 (Visit 13 of ZX008-1501 and ZX008-1502):

- Record demographic information
- Vital signs

- Record prior and concomitant medications (use core study Visit 13 information)
- Urine pregnancy test for females of child-bearing potential
- Tanner Staging for subjects >7 to ≤18 years of age (Appendix 5)
- Instruct parent/caregiver on use of diary
- Record ongoing AEs as medical history (use core study Visit 13 information)
- Record ongoing adverse events of special interest (AESIs) as medical history (use core study Visit 13 information)
- Dispense diary (after above procedures have been concluded)
- Dispense study medication

Data collected from Visit 12/End of Study for the core study may be used for the following procedures unless otherwise indicated:

- Record medical, neurological, and epilepsy history
- Complete physical examination, including height, weight, and calculation of body mass index (BMI)
- Complete neurological examination (use data collected at core study Visit 12, unless there was a significant change in subject status warranting a new complete examination)
- 12-lead ECG
- Doppler ECHO
- Laboratory evaluation (serum chemistry, hematology, urinalysis, etc) (use core study Visit 12 information, unless investigator determines new laboratory evaluation is warranted due to change in subject status)
- Urine THC panel
- Whole blood CBD
- Tanner Staging for subjects > 7 to ≤18 years of age (Appendix 5)
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6) (only for subjects from the core studies)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)

Affective symptoms of parent/caregiver using the HADS scale (Appendix 8). After enrollment into the study, each subject will be issued a new "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.

6.1.2.2 Clinic Visit 1 for Subjects from Core Study ZX008-1504

The following procedures will be performed during Visit 1(the last transition period of ZX008 1504 Cohort 1 and Visit 12 of ZX008-1504 Cohort 2):

- Record demographic information
- Vital signs
- Urine pregnancy test for females of child-bearing potential

Data collected from the last transition period of Cohort 1 and Visit 12/End of Study for Cohort 2 procedures may be used unless otherwise indicated:

- Record medical, neurological, and epilepsy history
- Record prior and concomitant medications
- Complete physical examination, including height, weight, and calculation of BMI
- Complete neurological examination (use core study Visit 12 information for subjects who participated in Cohort 2, and use core study information from the last transition period visit for subjects who participated in Cohort 1, unless there was a significant change in subject status warranting a new complete examination)
- 12-lead ECG
- Doppler ECHO
- Laboratory evaluation (serum chemistry, hematology, urinalysis, etc) (use data collected at core study Visit 12 for subjects who participated in Cohort 2, and use core study information from the last transition period visit for subjects who participated in Cohort 1, unless investigator determines new laboratory evaluation is warranted due to change in subject status)
- Urine THC panel
- Whole blood CBD
- Tanner Staging for subjects > 7 to ≤18 years of age (Appendix 5)
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6) (only for subjects from the core studies)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- Healthcare utilization questions
- Karolinska Sleepiness Scale (Appendix 10)
- Sleep quality and meal time behavior questions
- Instruct parent/caregiver on use of diary

- Record ongoing AEs as medical history
- Record ongoing AESIs as medical history
- Dispense diary (after above procedures have been concluded)
- Dispense study medication

After enrollment into the study, each subject will be issued a new "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.

6.1.3 Clinic/Phone Visit 2 (Study Day 15)

Visit 2 is to be performed in the clinic. At the discretion of the investigator, this visit may be performed via phone.

If Visit 2 is performed in the clinic, subjects will report to the clinic in the morning of that day. Subjects should not take their morning dose(s) of AED medication prior to reporting to the clinic. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications since previous visit
- Abbreviated physical examination, including height and weight, and calculation of BMI
- Abbreviated neurological examination
- Vital signs
- Laboratory evaluation (serum chemistry, hematology, urinalysis, etc) (only if investigator determines new laboratory evaluation is warranted due to change in subject status since Visit 1)
- Collect plasma sample for AED PK evaluation prior to the morning dose of study medication(s)
- Collect and review diary with parent/caregiver
- Dispense diary
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

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

- Concomitant medications

- AEs
- AESI
- Study medication use
- Diary entries

6.1.4 Clinic Visits 3-15 (Months, 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33)

Subjects will report to the clinic in the morning of Clinic Visits 3 through 15. Subjects should not take their morning dose(s) of AED prior to reporting to the clinic. The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Abbreviated physical examination, including height and weight, and calculation of BMI
- Abbreviated neurological examination
- Obtain vital signs
- 12-lead ECG
- Doppler ECHO (at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33)
- Urine pregnancy test for females of child-bearing potential
- Laboratory evaluation (serum chemistry and hematology, and urinalysis)
- Urine THC panel
- Whole blood CBD
- Collect plasma sample for AED PK evaluation prior to the morning dose of study medication(s)
- Tanner Staging for subjects > 7 to ≤18 years of age (Visits 6, 15, and 27 only) (Appendix 5)
- Collect and review diary with parent/caregiver
- Dispense diary
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6) (only for subjects from the core studies)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- Affective symptoms of parent/caregiver using the HADS scale (Appendix 8) (for subjects from core studies ZX008-1501 and ZX008-1502 only)
- Healthcare utilization questions (for subjects from core study ZX008-1504 only)
- Karolinska Sleepiness Scale (Appendix 10) (for subjects from core study ZX008-1504 only)

- Sleep quality and mealtime behavior questions (for subjects from core study ZX008-1504 only)
- Study medication palatability assessment (Visits 3 and 4 only)
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication

6.1.5 Clinic Visit 16 (Month 36): End of Study/Early Termination

The End-of-Study participation for an individual subject occurs after he/she has received IMP for 3 years in the OLE Treatment Period or if the subject is transitioning to receive ZX008 in a separate extension protocol when available or until 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 one the following events occur:

1. The subject withdraws or is withdrawn from participation in the study.
2. The Sponsor terminates the study.
3. The subject completes all study related visits and procedures.
4. The subject is being transitioned to another extension study or transitioning to commercially available drug.

The following procedures will be performed:

- Review current seizure activity (number/type/duration) from diary since previous visit
- Record concomitant medications
- Complete physical examination, including height and weight, and calculation of BMI
- Complete neurological examination
- Obtain vital signs
- 12-lead ECG
- Doppler ECHO (must be performed any time between Study Day 1064 and Study Day 1085; if subject terminates early from the study, the ECHO should be scheduled as soon as practical). If the Month 3, 6, 9, 12,1 5, 18, 21, 24, 27, 30, or 33 ECHO was completed ≤ 30 days prior to early termination, the Visit 12 ECHO will not be performed provided the parent/guardian agrees to bring the subject to the clinic for the cardiac follow-up visit (Table 8).
- Urine pregnancy test for females of child-bearing potential

- Laboratory evaluation (serum chemistry and hematology, and urinalysis)
- Urine THC panel
- Whole blood CBD
- Collect plasma sample for AED PK evaluation prior to the morning dose of study medication(s)
- Tanner Staging for subjects > 7 to ≤18 years of age (Appendix 5)
- Collect and review diary with parent/caregiver
- C-SSRS Children's Since Last Visit Assessment (Appendix 2)
- CGI-I (assessed by parent/caregiver)
- CGI-I (assessed by investigator)
- BRIEF (Appendix 3)
- QOLCE (Appendix 4)
- PedsQL (Appendix 6) (only for subjects from the core studies)
- Parent/Caregiver QoL using the EQ-5D-5L scale (Appendix 7)
- Affective symptoms of parent/caregiver using the HADS scale (Appendix 8) (for subjects from core studies ZX008-1501 and ZX008-1502 only)
- Healthcare utilization questions (for subjects from core study ZX008-1504 only)
- Karolinska Sleepiness Scale (Appendix 10) (for subjects from core study ZX008-1504 only)
- Sleep quality and mealtime behavior questions (for subjects from core study ZX008-1504 only)
- Record AEs
- Record AESI
- Collect used, partially used and unused study medication; perform drug accountability and review with parent/caregiver
- Dispense study medication (not applicable for subjects transitioning to another extension protocol or to commercial drug)

6.2 POST-DOSE VISIT (CLINIC VISIT 17; STUDY DAY 1099)

If the subject completes the study (or discontinues from the study early), and is not transitioning to another extension protocol or switching to commercially available drug, the subject will visit the clinic on Study Day 1099 (or 14 days after the day of discontinuation)

The following procedures will be performed:

- Record AEs
- Record AESI
- Record concomitant medications

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

6.3 CARDIAC FOLLOW-UP VISIT (CLINIC VISIT 18, 19; 3 AND 6 MONTHS) AFTER LAST DOSE OF IMP

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 8. 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. Cardiac follow-up visits are not required for subjects who have entered another ZX008 extension study or have transitioned to commercial drug.

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.

If the subject is switching to commercially available drug, (subjects must have an ECHO within 3-6 months before starting commercial 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 post dosing and cardiac follow-up visits are not required.

Table 8. Schedule of Post-Treatment Cardiac Follow-up

Parameter	Duration of Fenfluramine Treatment				
	Less than 2 weeks Cumulative	**2 to 4 weeks**	**> 4 and < 13 weeks**	**> 13 weeks**	**Have had any cardiac sign or symptom regardless of the time on study drug[a]**
ECHO	No	Yes, 3 months post-treatment	Yes, 3 months post-treatment	Yes, 3 and 6 months post-treatment	Yes, 3 and 6 months post-treatment, and until resolved, or stable and unlikely to change
ECG	No	Yes, 3 months post-treatment	Yes, 3 months post-treatment	Yes, 3 and 6 months post-treatment	Yes, 3 and 6 months post-treatment and until resolved, or stable and unlikely to change
Physical examination	No	Yes, 3 months post-treatment	Yes, 3 months post-treatment	Yes, 3 months post-treatment only	Yes, 3 and 6 months post-treatment, and until resolved, or stable and unlikely to change

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

6.4 ESTIMATED BLOOD VOLUME COLLECTION

The maximum total blood volume collected during the study for clinical laboratory testing, genotyping, and PK will be approximately 240.0 mL, as outlined in Table 9.

Table 9. Estimated Blood Volume Collection[a]

Assessment/ (Study Day)	OLE Treatment Period (study day)		
	15	**30, 60, 90. 180, 270. 365, 455, 545, 635, 725, 815, 905, 995, 1085**	**Total**
Clinical chemistry	--	7.5 mL at each visit	105 mL
LH, FSH, estradiol, testosterone, GH, prolactin	--	Included in Chemistry	
Hematology	--	2 mL at each visit	28 mL
IGF-1	--	3.5 mL at each visit	49 mL
Cannabidiol	--	2 mL at each visit	28 mL
AED plasma sample	1 x 2 mL	1 x 2 mL at each visit	30 mL
Approximate total blood volume per subject	2.0 mL	17.0 mL at each visit	**240.0 mL**

FSH=follicle stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; LH-luteinizing hormone

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

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

6.5 STUDY CONDUCT DURING COVD-19

In March 2020, the World Health Organization declared a global pandemic related to an illness caused by a novel coronavirus known as COVID-19. Alternative procedures and allowances are permitted due to restrictions related to COVID-19, including delays to in-person visits and specific assessments, performing remote phone or video visits if in-person visits cannot be conducted, and arranging shipments of investigational product directly to subjects. These allowances are detailed in Appendix 11. Though every attempt should be made to conduct study visits as described in this protocol, any implementation of alternative processes should be properly documented, including what was done differently, which assessments or visits were missed or performed via phone or video.

7. EFFECTIVENESS, SAFETY, AND PHARMACOKINETIC ASSESSMENTS

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

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

7.1 EFFECTIVENESS ASSESSMENTS

For all questionnaires and rating scales, 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 questionnaires and rating scales completed by the parent/caregiver, if the same parent/caregiver cannot complete the questionnaire/rating scale at a visit, the questionnaire/rating scale will not be completed. For the diary, the same parent/caregiver will complete all entries throughout the study.

7.1.1 Seizure Assessments

Seizure frequency by type and duration (< 2 minutes, 2-10 minutes, > 10 minutes) will be recorded daily by the parent/caregiver in a diary. Seizure types include:

A: Hemiclonic (note lateralization – right body, left body, or independent right and left)
B1: Focal With or Without Clear, Observable Motor Signs
B2: Focal Without Clear, Observable Motor Signs
C: Secondarily Generalized Tonic Clonic (evolving to bilateral convulsive seizure from focal seizure)
D: Generalized Tonic Clonic Convulsion
E: Absence or Atypical Absence
F: Myoclonic
G: Tonic
H: Atonic
I: Clonic
J: Tonic/Atonic (cannot differentiate; also known as ‘drop attack’)
K: Infantile Spasms (if under 3 years of age)
L: Epileptic Spasms (if 3 years of age and older)
O: Other

Effectiveness endpoints that will be derived from the diary data include frequency of convulsive seizures and of all seizures, and the number/duration of seizure free intervals.

Seizures that evolve into SE will be captured by type and duration (> 10 minutes) as are all seizures. The diagnosis of SE should be entered as an AE or SAE if a prolonged seizure or series of seizures persists for 30 minutes or longer, regardless of administration of rescue medication. If this incident involves multiple seizures close in time, the SE definition applies if the seizures are close together such that consciousness is not regained between ictal events.

7.1.2 Clinical Global Impression - Improvement

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

The 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 severity of a patient's condition is rated on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) as follows:

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

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

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

7.1.3 Quality of Life in Childhood Epilepsy Scale

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

7.1.4 Pediatric Quality of Life Inventory (PedsQL)

The PedsQL (Appendix 6) is a pediatric modular measure of health-related QoL completed by the parent/caregiver on behalf of the subject. It consists of 4 core scales that measure physical, emotional, social, and school functioning. The PedsQL will be conducted according to the schedule in Table 1 and Table 2. The PedsQL will only be conducted in subjects who enter from the core studies (ie, PedQL will not be performed on de novo subjects >18 years of age).

7.1.5 Parent/Caregiver Quality of Life

The impact on the quality of life of the parent/caregiver responsible for a patient with DS will be assessed according to the schedule in Table 1 and Table 2 using 3 scales: the EQ-5D-5L, the HADS, and the PedsQL Family Impact Module. Parents/caregivers who do not give consent to collect these ratings scales will not complete them. The same parent/caregiver should complete these ratings throughout the study. If that person is not available at the visit, the scales should not be completed.

The EQ-5D-5L (Appendix 7) is a standardized measure of health status used to provide a simple, generic assessment for clinical and economic appraisal. It consists of 6 questions and can be completed in less than 10 minutes.

The HADS (Appendix 8) is a tool commonly used to determine the levels of anxiety and depression that a person is experiencing. It is a 14-item scale that generates ordinal data. Seven of the items relate to anxiety and 7 relate to depression.

The PedsQL Family Impact module (Appendix 6) is designed to measure the impact of pediatric chronic health conditions on parents and the family by measuring parent self-reported physical, emotional, social, and cognitive functioning, communication, worry, and family daily activities relationships. The PedsQL Family Impact module will not be assessed in the Netherlands.

The parent/caregiver will be asked to indicate the appropriate response that adequately describes how the care of their child with DS has impacted their quality of life using the scales described above.

7.1.6 Study Medication Palatability Assessment

The palatability and overall acceptability of the IMP will be assessed indirectly by the parent/caregiver responsible for the patient according to the schedule in Table 1 and Table 2 using 3 questions:

QUESTION 1: Over the past month, on the basis of the reaction/facial expression of your child, do you think that the medicine's taste and texture are:

- Acceptable to your child
- Not acceptable to your child

QUESTION 2: Over the past month, please rate how much your child likes/dislikes the medicine's taste using the following grading scale:

- 5 (likes it very much)
- 4 (likes it)
- 3 (neither likes it or dislikes)
- 2 (dislikes it)
- 1 (dislikes it very much)

QUESTION 3: Over the past month, do you sometimes have problems giving the medicine to your child due to its taste or texture?

- No
- Yes
    - How often?
        - Every day in the past month
        - Once to several times every week in the past month
        - Once or several times in the past month

7.2 EXPLORATORY ASSESSMENTS

The following exploratory assessments will be conducted for subjects who participated in core study ZX008-1504 only.

7.2.1 Sleep Quality and Meal Time Behavior Questions

The parent/caregiver will be asked to indicate the appropriate response that adequately describes their child's sleep quality and eating behavior since starting IMP based on the following questions:

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

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

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

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

7.2.2 Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale (Appendix 10) will be administered according to the schedule in Table 2. The Karolinska Sleepiness scale is a self-report scale that measures the subject's drowsiness. It is a 9-point verbally anchored scale, which ranges from 'extremely alert' at one end of the scale to 'extremely sleepy – fighting sleep' at the other end of the scale. Within this study, the scale will be completed by the observer in an exploratory manner.

7.2.3 Healthcare Utilization Questions

In order to better understand the healthcare resource burden associated with the management of DS, caregivers will be asked which of the following hospital and community-based healthcare services they had interactions with over the preceding month: emergency room services, ambulance, planned and unplanned hospitalization, family physician services, speech and language therapy, occupational therapy, and physical therapy. This information will be captured in the CRF.

7.3 SAFETY ASSESSMENTS

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

Subject demographics (sex, age, height, weight, and BMI), all ongoing conditions and relevant medical history from the past 5 years (including all major hospitalizations and surgeries) as well as the subject's current medical status and current medications will be carried over from the core study.

7.3.2 Physical Examinations

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

Any unfavorable findings not present at Visit 12 of the core study considered by the investigator as clinically significant, occurring at any point in the study will be documented in the CRF as an AE.

7.3.3 Neurological Examinations

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

7.3.4 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 and Table 2.

7.3.5 Laboratory Measurements

Laboratory safety parameters will be analyzed using standard validated methods.

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

- 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), thyroid function (T3, T4, and thyroid stimulating hormone [TSH]), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid.

- Tests of growth and precocious puberty: growth hormone (GH), insulin-like growth factor-1 (IGF-1, low sensitivity), prolactin, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, estradiol

- Whole blood cannabidiol
- Urinalysis: analysis for pH, glucose, ketones, nitrite, protein, bilirubin, urobilinogen, leukocyte esterase, and occult blood. Microscopic analysis will be performed for blood, all cell types, and casts.
- Urine pregnancy test: Urine pregnancy testing will be performed in female subjects of childbearing potential.
- Urine THC panel

The investigator will receive the laboratory report from the central laboratory. After reviewing the report and evaluating any results that are outside the normal range, 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).

7.3.6 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 as outlined in Table 1 and Table 2. All samples will be analyzed at study end and do not constitute safety assessments.

7.3.7 Electrocardiograms

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

7.3.8 Doppler Echocardiography

Doppler echocardiography will be conducted at a facility with experience for the subject's age during study as outlined in Table 1 and Table 2. Doppler echocardiography uses ultrasound technology to examine the heart or blood vessels. An ECHO uses high frequency sound waves to create an image of the heart while the use of Doppler technology allows determination of the speed and direction of blood flow by utilizing the Doppler effect. Predetermined standard

guidelines on the proper evaluation of certain measurements, as well as abnormality thresholds, were constructed by the Sponsor's IPCAB prior to study initiation. These thresholds are provided in Table 10 (Adverse Events of Special Interest). A manual of proper ECHO technique for sites is provided in a separate document.

7.3.9 Tanner Staging

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

7.3.10 Columbia-Suicide Severity Rating Scale

C-SSRS (Appendix 2) will be assessed during study as outlined in Table 1 and Table 2. The C-SSRS is a validated rating scale that assesses suicidal behavior and ideation. The scale is used to assess and track suicide events and provides a summary measure of suicidal tendency. The C-SSRS version 6/23/10 (Children's 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.

7.3.11 Adverse Events

For de novo subjects, 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 one 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 ZX008-1503.

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.

7.3.12 Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF is a standardized, validated rating scale to measure executive function. Age-appropriate versions of the BRIEF (BRIEF-P: 2 to 5 year olds; BRIEF: 6 to 18 year olds; BRIEF-A: 19 to 35 year olds) will be assessed according to the schedule in Table 1 and Table 2. The BRIEF measures multiple aspects of executive functioning; scales include Inhibit (control impulses; stop behavior), Shift (move freely from one activity/situation to another; transition; problem-solving flexibility), Emotional Control (modulate emotional responses appropriately), Initiate (begin activity; generate ideas), Working Memory (hold information in mind for purpose of completing task), Plan/Organize/Organization of Materials (anticipate future events; set goals; develop steps; grasp main ideas), and Monitor (check work; assess own performance).

7.4 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. For de novo subjects, the period of observation for adverse events extends from the time the subject gives informed consent until the end of study. For subjects who participated in one of the core studies, the period of observation for adverse events extends from Visit 1 of ZX008-1503 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 ZX008-1503.

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 Visit 13 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 one of the above outcomes listed as an SAE criterion. Anaphylaxis that is successfully treated by administration of epinephrine prior to other sequelae is an example of a potentially medically important event.

   - The most important term should be selected as the criteria for the SAE. Medically significant should be used when none of the other terms apply, for cases in which, had there not been intervention, one of the other SAE outcomes would have likely occurred. For example, anaphylaxis successfully treated with an epinephrine injection would be a medically important event.

   - 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 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 as well as in the seizure diary. If two 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 non-serious AEs.

8.1.3 Adverse Events of Special Interest

As per ICH guidance (E2F Development Safety Update Report [2011]), the Sponsor has identified the following AESIs for the ZX008 program (Table 10).

Table 10. Adverse Events of Special Interest

Metabolic/Endocrine
1. Elevated prolactin level ≥ 2x above the upper limit of normal (ULN)
2. Hypoglycemia – serum blood glucose more than 20% below the glucose level on Study Day -1 value or more than 10% below LLN (reference range 60 – 140 mg/dL)
Neuropsychiatric
1. Suicidal thoughts, ideation or gestures

LLN = lower limit of normal; ULN = upper limit of normal

8.1.4 Adverse Events Requiring Hospitalization

If a subject is treated in a medical facility (hospital, emergency room, free-standing clinic) related to the occurrence of any AE, the following data will be collected to model health care utilization in patients with DS: AE/reason for hospitalization/clinic visit; duration of the visit in hours/days; admission to intensive care unit; and name/number of procedures performed, including but not limited to, electroencephalogram, ECG, ECHO, positive emission tomography (PET) scan, magnetic resonance imaging (MRI), x-ray, computed tomography (CT) scan, surgery, and lumbar puncture/spinal tap.

8.2 SEVERITY OF ADVERSE EVENTS

The severity of AEs (whether non-serious or serious AEs) is to be assessed by the investigator as follows (Table 11).

Table 11. 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 for de novo subjects will start at the time of giving written informed consent for participation in the current study and finish 15 days after the last dose of study drug or the last visit, whichever is later. For subjects who participated in one of the core studies, the observation period for adverse events will start at Visit 1 of 1503 and finish 15 days after the last dose of study drug or the last visit, whichever is later. 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.

8.6 SERIOUS ADVERSE EVENTS REPORTING

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

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

1. Enter all relevant information in the AE page of the eCRF.
2. Inform the Medical Monitor or the Sponsor of the SAE via email or telephone within 24 hours of becoming aware of the SAE.
3. Follow the initial notification with a completed SAE report form. The SAE form must be emailed or faxed to Inventive Health Care within 24 hours of becoming aware of the SAE.

All SAEs that occur during the course of the study, beginning the day Informed Consent is signed for de novo subjects and at Visit 1 for subjects from the core studies, whether or not causally related to IMP must be reported immediately via telephone or email (within 24 hours of the investigator becoming aware of the event) to the Sponsor or the Medical Monitor.

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

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

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

8.6.1 Requirements for Immediate Reporting of Serious Adverse Events

The minimum reporting requirements for immediate reporting of SAEs include:

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

In addition, the investigator must:

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

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 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 Medical Monitor. In the event of a SAE, a blood sample for ZX008 and AED PK should be collected as soon as feasible.

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 BioMedical Systems, Inc. (BMS), in consultation with the IPCAB, if warranted. Findings related to pulmonary hypertension or valvulopathy on any of the four valves (aortic, mitral, pulmonary, tricuspid) will be reported to the investigator with grades of normal, trace, mild, moderate, or severe. If the ECHO result has progressed in severity since the last reading, then new oversight measures will be enacted as described below in Levels 1-3. Table 12 describes the severity of ECHO findings with the level of increasing oversight if the subject is to remain in the study.

Table 12. Clinical Measures Enacted Upon Increasing Severity of ECHO Findings

Severity	Valve			
	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 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 for review, including consideration of effects on seizures and comorbidities.
4. The Co-Chairs of the IPCAB are alerted to the request and prepare, after consultation with BMS, an evaluation of the cardiopulmonary risk and proposed monitoring plan if applicable, for submission to the IDSMC.
5. IDSMC will review the submission from the Investigator and the IPCAB and unblind the subject's core study treatment, if warranted.
6. IDSMC makes a determination of appropriate path, including the possible outcomes:
    a. Discontinue study medication
    b. Increase frequency of ECHO and ECG monitoring
    c. Add additional ECG and/or ECHO measures to be monitored
    d. Reduce the dose of study medication

Level 3:

1. The investigator will evaluate efficacy to date based on study diaries and consult with the parent/guardian, and determine whether the achieved benefit justifies the consideration of continuing study treatment by the IDSMC. MINIMAL efficacy criteria for IDSMC consideration:
    a. Seizures must be more than 75% improved (number of 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 for review, which includes effects of study medication on seizures and comorbidities related to DS.
4. The Co-Chairs of the IPCAB are alerted to the request, and in consultation with BMS prepare an evaluation of the risks and proposed monitoring plan if applicable for submission to the IDSMC.

5. IDSMC will review the submission from the Investigator and the IPCAB and unblind the subject's core study treatment, if warranted.
6. IDSMC makes a determination of appropriate path, including these possible outcomes:
    a. Discontinue study medication
    b. Increase frequency of ECHO and ECG monitoring
    c. Add additional ECG and/or ECHO measures to be monitored
    d. Reduce the dose of study medication

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

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

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

9.2 DATA QUALITY ASSURANCE

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

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

The computer system used for study data handling will be fully 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 1 of 3 core studies (Study ZX008-1501, Study ZX008-1502, or Study ZX008-1504) and who volunteer for the extension study and meet the necessary criteria for enrollment. Approximately 100-120 subjects are expected to participate in each of the core studies; thus, if all participants also enroll in the extension, the total sample size of the extension study would be approximately 340.

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 one dose of ZX008 during the 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 one dose of ZX008 and have valid seizure data during the open label extension. Effectiveness analyses, such as evaluating the change in the frequency of convulsive seizures, 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 one dose of ZX008, complete the entire OLE Treatment Period of the open label extension, and have no major protocol deviations that would have a significant impact on clinical outcome. Key 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

For subjects who receive ZX008 in Study ZX008-1501, Study ZX008-1502, or Study ZX008-1504 Cohort 2, the pre-ZX008 baseline period is equivalent to the core study pre-

randomization baseline period, ie, the approximately 42-day span just prior to randomization and start of treatment in the core study.

For subjects who receive placebo in Study ZX008-1501, Study ZX008-1502, or Study ZX008-1504 Cohort 2, the pre-ZX008 baseline period begins with the core study pre-randomization baseline period and extends through the entire span of the core study up to the transition period. The pre-ZX008 baseline period for a subject ends when that subject receives their first treatment with ZX008.

Study ZX008-1504 Cohort 1 have a shortened (exploratory) baseline period of approximately 12 days (after the single-dose PK assessment) and this will be used in an exploratory manner.

For de novo subjects, the pre-ZX008 baseline period is the screening period of up to 28 days prior to receiving the first dose.

The baseline frequency of convulsive seizures will be calculated from data collected during the entire length of the pre-ZX008 baseline period.

Open-Label Extension Treatment Period

The OLE Treatment Period covers the 36 months during which subjects will receive open label treatment with ZX008.

Post-dosing Period

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

After at least 1 year of treatment in Study 1503 subjects who participated in one of the core studies will transition to a separate extension study (Study 1900) once that study is approved and the study site is initiated. Continuation in a separate extension protocol will be based on benefit/risk and continued eligibility criteria being met. De novo subjects must have participated in this trial for at least 3 months with at least 1 ECHO completed and continue to meet eligibility requirements to be eligible to transition to a separate extension protocol. Alternatively, subjects will transition to commercial product once it is available if they have had an ECHO within 3-6 months before starting commercial drug. For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial. Subjects who transition to commercially available drug will have follow-up ECHOs within the required timeframe while on commercial drug.

10.5 STATISTICAL ANALYSES AND METHODS

All safety, effectiveness and exploratory 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 each core study and 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 and ≥ 6 years.

Hematology and chemistry laboratory results will be summarized using shift tables that tabulate the proportion of subjects who have lab results that change from pre-ZX008 baseline, where pre-ZX008 baseline values will be determined from lab results obtained prior to first treatment with ZX008. The shift tables will be presented for each time point where lab results are collected. Mean change from pre-ZX008 baseline will also be calculated for continuous hematology and chemistry results at all time points available.

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 Key Effectiveness Analysis

The key effectiveness endpoint is the change in the convulsive seizure frequency per 28 days between the pre-ZX008 Baseline and OLE Treatment Period. The frequency of convulsive seizures during a given period will be derived from the number and type of events recorded in subject diaries. The seizure frequency per 28 days will be calculated as the number of seizures recorded divided by the number of days in the period and multiplied by 28. The convulsive

seizure frequency will be calculated from all available data collected during either the pre-ZX008 Baseline or OLE Treatment Periods.

Both the mean and median frequency of convulsive seizures will be presented for the pre-ZX008 Baseline Period and the OLE Treatment Period. The significance of the change between periods will be assessed using an analysis of covariance (ANCOVA) model with age group (< 6 years, ≥ 6 years) as a factor and with pre-ZX008 baseline frequency as a covariate. Other factors may be included in the model if they are found to be informative during analyses of the core studies.

Since the ANCOVA relies on assumptions of normality, the key effectiveness endpoint will also be analyzed using a nonparametric method that does not require as stringent assumptions. A test such as the stratified Wilcoxon signed rank test will be used to assess the change from baseline while stratifying by age group.

An additional analysis will be performed to assess the sensitivity of the key effectiveness analysis to changes in dose or type of concomitant AED medications that may occur during the course of the trial. Specifically, the analysis will be repeated with a factor added to the model to indicate whether a subject had a change in prescribed dose or type of concomitant AED medication during the OLE Treatment Period. Further exploratory analyses may be conducted if changes in concomitant AED medication appear to have a significant impact on the effectiveness of ZX008.

Only subjects from Studies ZX008-1501, ZX008-1502, and Cohort 2 of ZX008-1504 will be included in change from baseline analyses of effectiveness. Subjects from Study ZX008-1504 Cohort 1 will be excluded from such analyses since they will enter the OLE Treatment Period without first participating in a baseline period that includes a formal assessment of pre-ZX008 seizure frequency.

10.5.2.2 Other Secondary Analyses

Methods similar to those used for the key effectiveness analysis will also be used to assess the change in frequency of non-convulsive seizures and the composite endpoint of non-convulsive plus convulsive seizures. The proportion of subjects who achieve a ≥40% reduction from baseline in convulsive seizure frequency, along with its 95% CI, will be reported. A similar summary will be reported for the proportion of subjects who achieve a ≥50% reduction from baseline. The analyses will be performed using data collected over the open label OLE Treatment Period.

The longest interval between convulsive seizures will be calculated for each subject over the entire OLE Treatment Period. The median interval will be presented.

Palatability will be assessed through descriptive statistical methods. For example, the percentage of parents or caregivers who consider the medicine's taste and texture to be acceptable to the subject will be presented along with a 95% CI at each time point data are available.

QoL measures will be summarized by descriptive statistic for each time point where they are obtained. Where appropriate, the significance of the change from baseline will be assessed using mixed effects models for repeated measures.

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.

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.

11.3 REGULATORY CONSIDERATIONS AND INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

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

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

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

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

11.4 PROTOCOL COMPLIANCE

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

The investigator should not implement any deviation from, or changes to, the study protocol without agreement by the Sponsor (delegate) and prior review and documented approval or favorable opinion from the IEC/IRB of an amendment to the study protocol. Exceptions include

only cases of medical emergency to address immediate hazards to study subjects, or when the changes involve only logistic or administrative aspects of the study.

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

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

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

At the earliest opportunity, the investigator (or delegate) must inform the Sponsor (delegate) about any notable protocol deviations and explain any deviation from the approved study protocol in the 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 one 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.

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 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 "non-substantial" 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 non-substantial protocol amendments. The substantial and non-substantial protocol amendments will be integrated into an updated study protocol at the discretion of the Sponsor if the changes to the original study protocol are numerous, or if required by applicable regulatory requirements.

12.11 AUDITS AND INSPECTIONS

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

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

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

12.12 CLINICAL STUDY REPORT

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

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

12.13 USE OF DATA AND PUBLICATIONS

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

For multicenter studies, the first publication must be based upon all data obtained from all analyses, as stipulated in the study protocol by the biostatistician and not by the investigators. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of study sites before the full, initial publication is available or 5 years after the last clinical study visit, whichever is later, unless this has been agreed to by all other investigators and by the Sponsor.

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

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ZX008 Investigator's Brochure Version 8.

14. APPENDICES

14.1 APPENDIX 1 – LIST OF PROHIBITED CONCOMITANT MEDICATIONS

alfentanil	mexiletine
almotriptan	naratriptan
alprenolol	nefazodone
amitriptyline	nortriptyline
amphetamine	ondansetron
astemizole	oxcarbazepine
atomoxetine	oxycodone
bufuralol	paroxetine
bupropion	perphenazine
buspirone	phenacetin
cafergot	phenobarbital
cannabidiol	phenytoin
carbamazepine	promethazine
cerivastatin	propafenone
citalopram	retigabine/ezogabine
clomipramine	risperidone
codeine	ritonavir
cyproheptadine	rizatriptan
desipramine	selegiline
dextromethorphan	sertraline
duloxetine	sumatriptan
eletriptan	telaprevir
encainide	thc and derivatives
ergotamine tartrate	tramadol
eslicarbazepine	trazodone
felbamate	vortioxetine
fentanyl	zolmitriptan
fluoxetine	zuclopenthixol
fluvoxamine	
frovatriptan	
imipramine	
levacetylmethadol (laam)	
linezolid	
meperidine	
methadone	
metoclopramide	

14.2 APPENDIX 2 – COLUMBIA – SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Baseline/Screening

Version 6/23/10

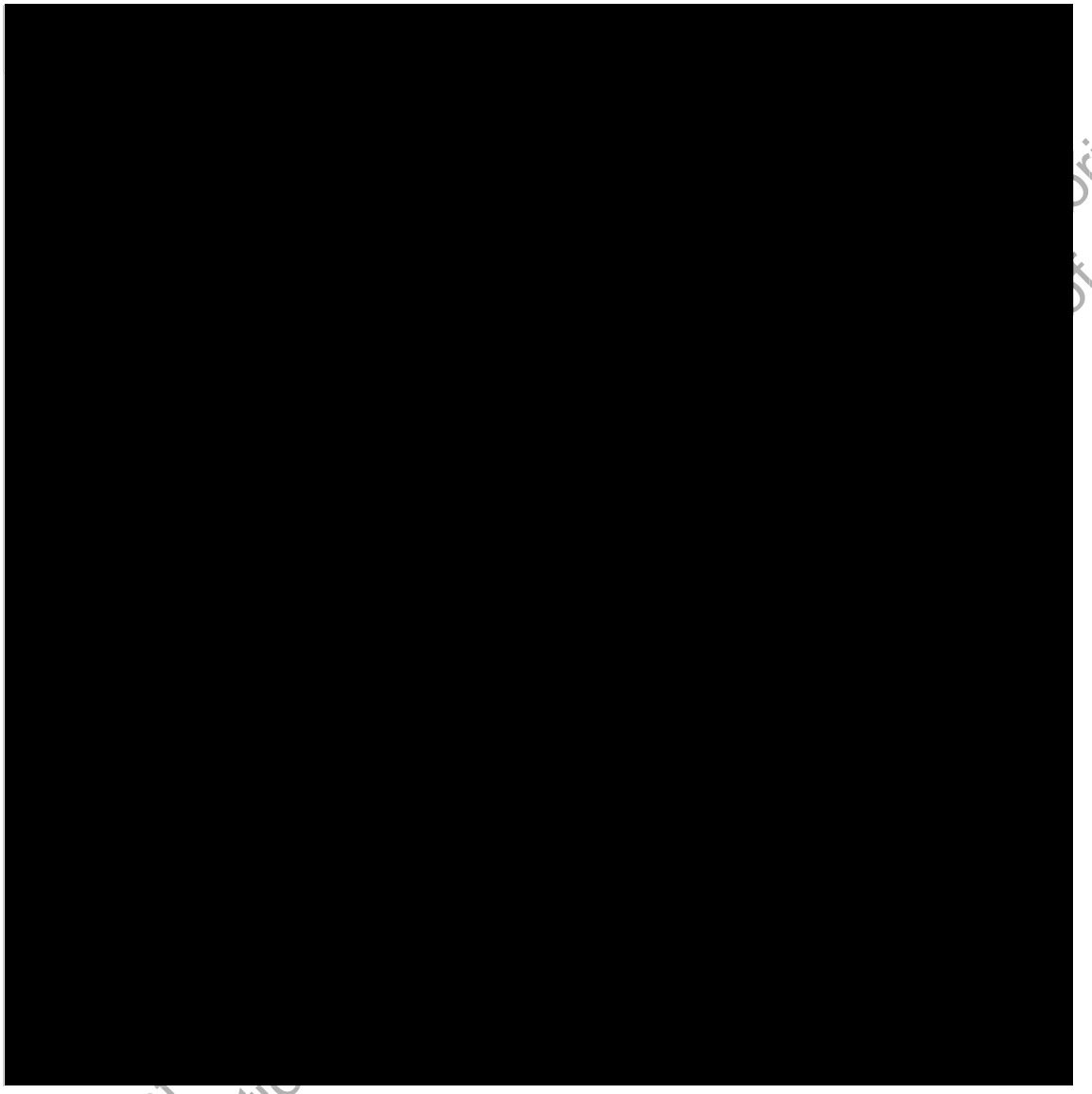
Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

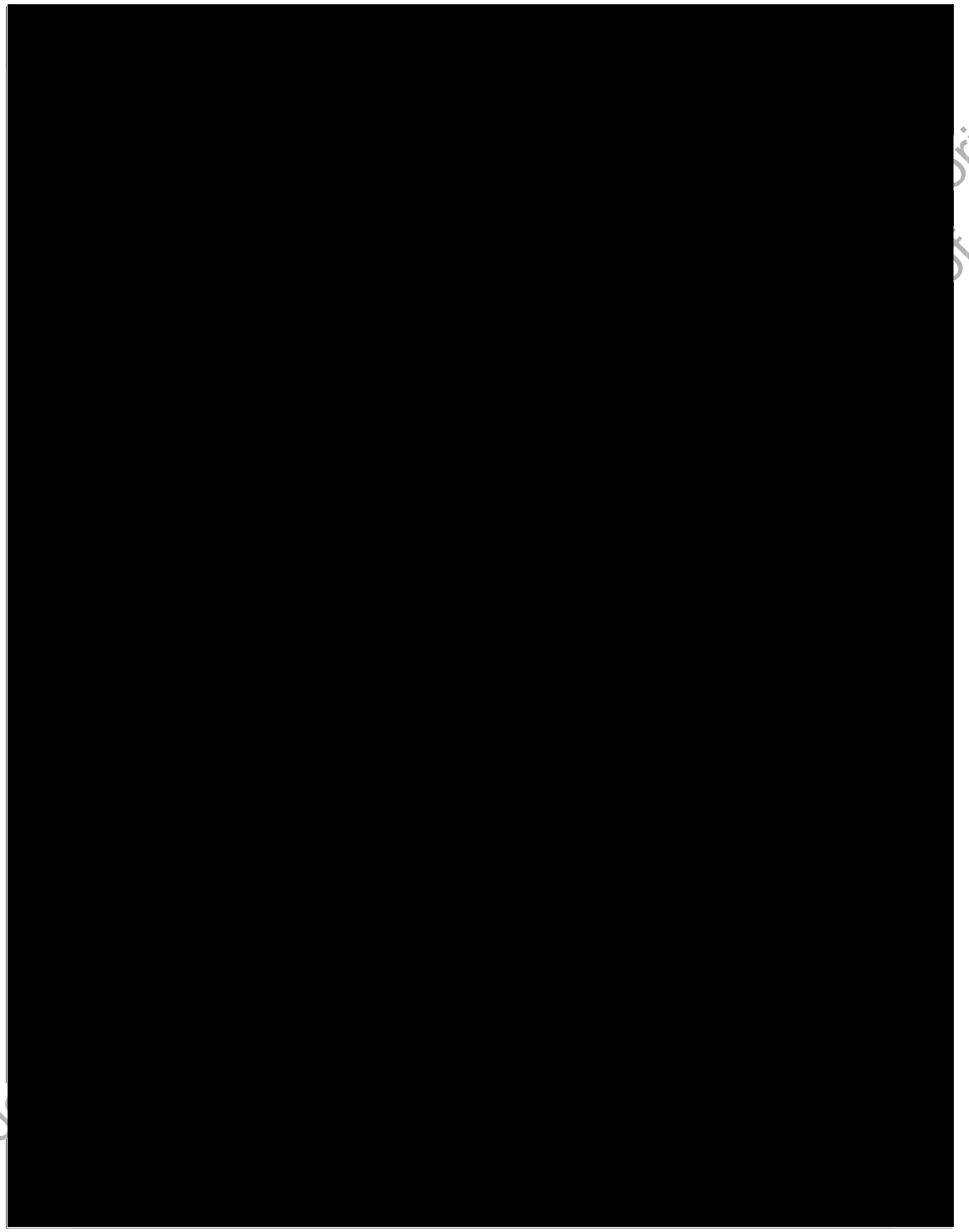
This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the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

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

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



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



COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Children's Since Last Visit

Version 6/23/10

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

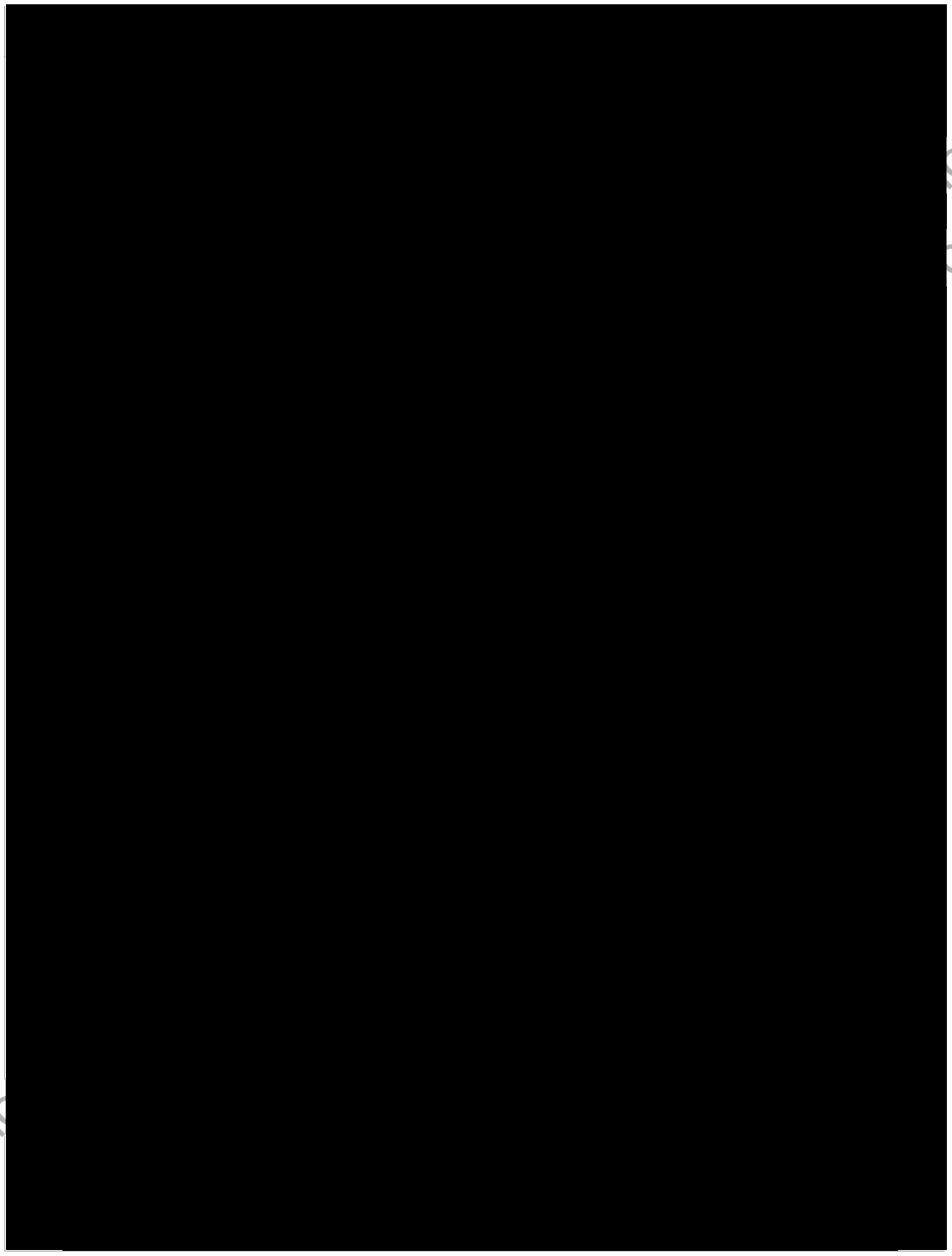
Disclaimer:

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

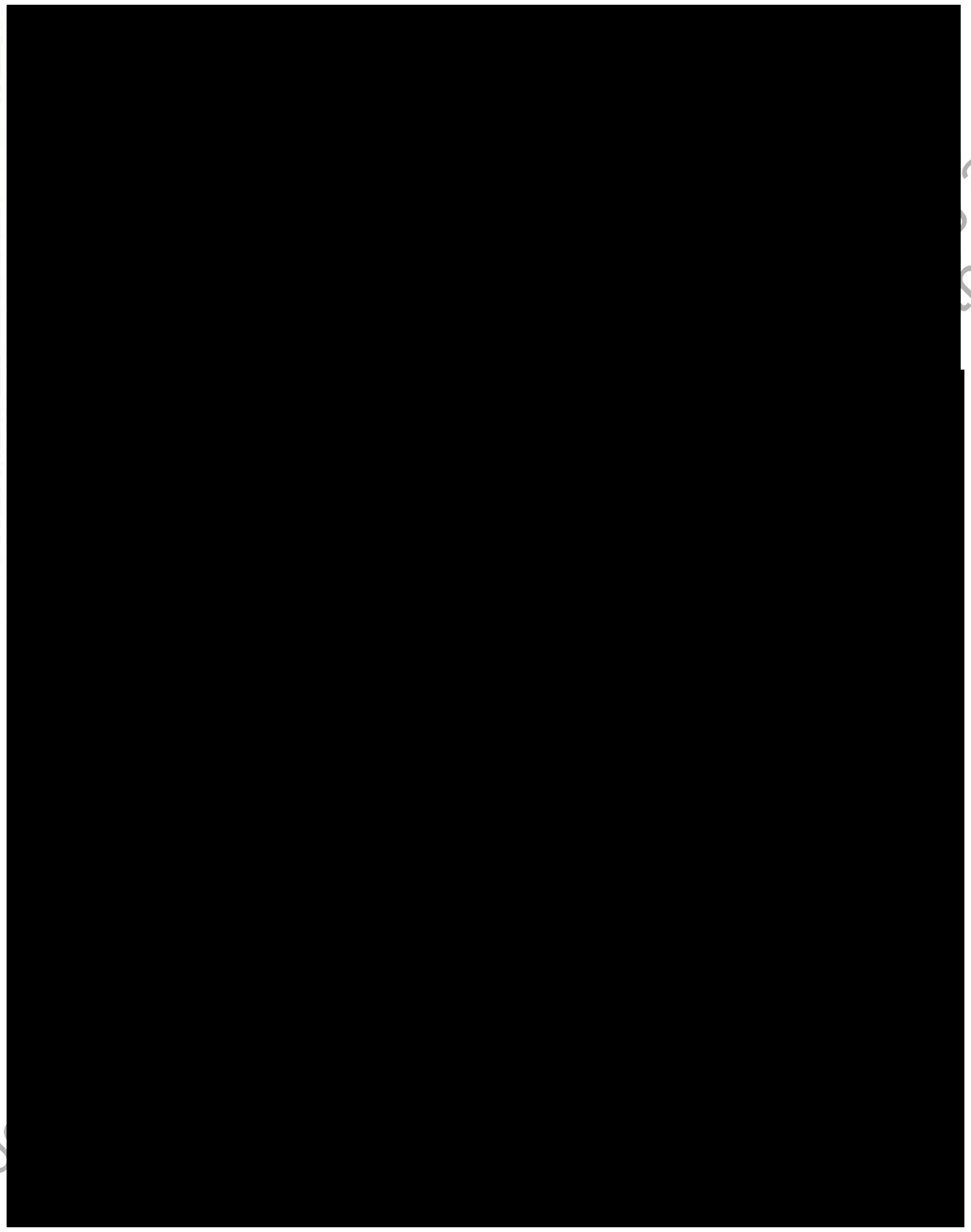
Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New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

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

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



14.3 APPENDIX 3 – BEHAVIOR RATING INVENTORY OF EXECUTIVE FUNCTION – PRESCHOOL VERSION



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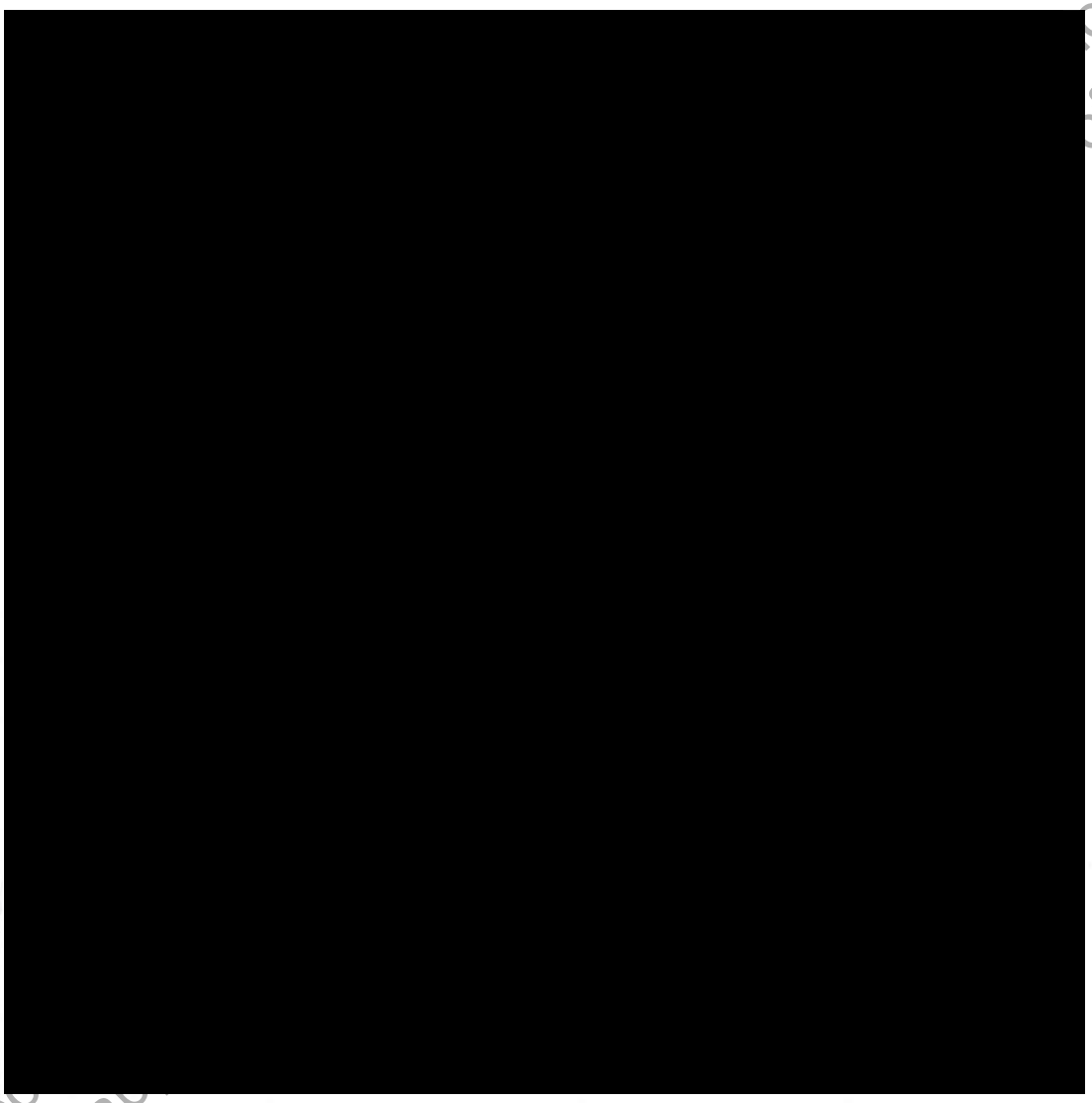

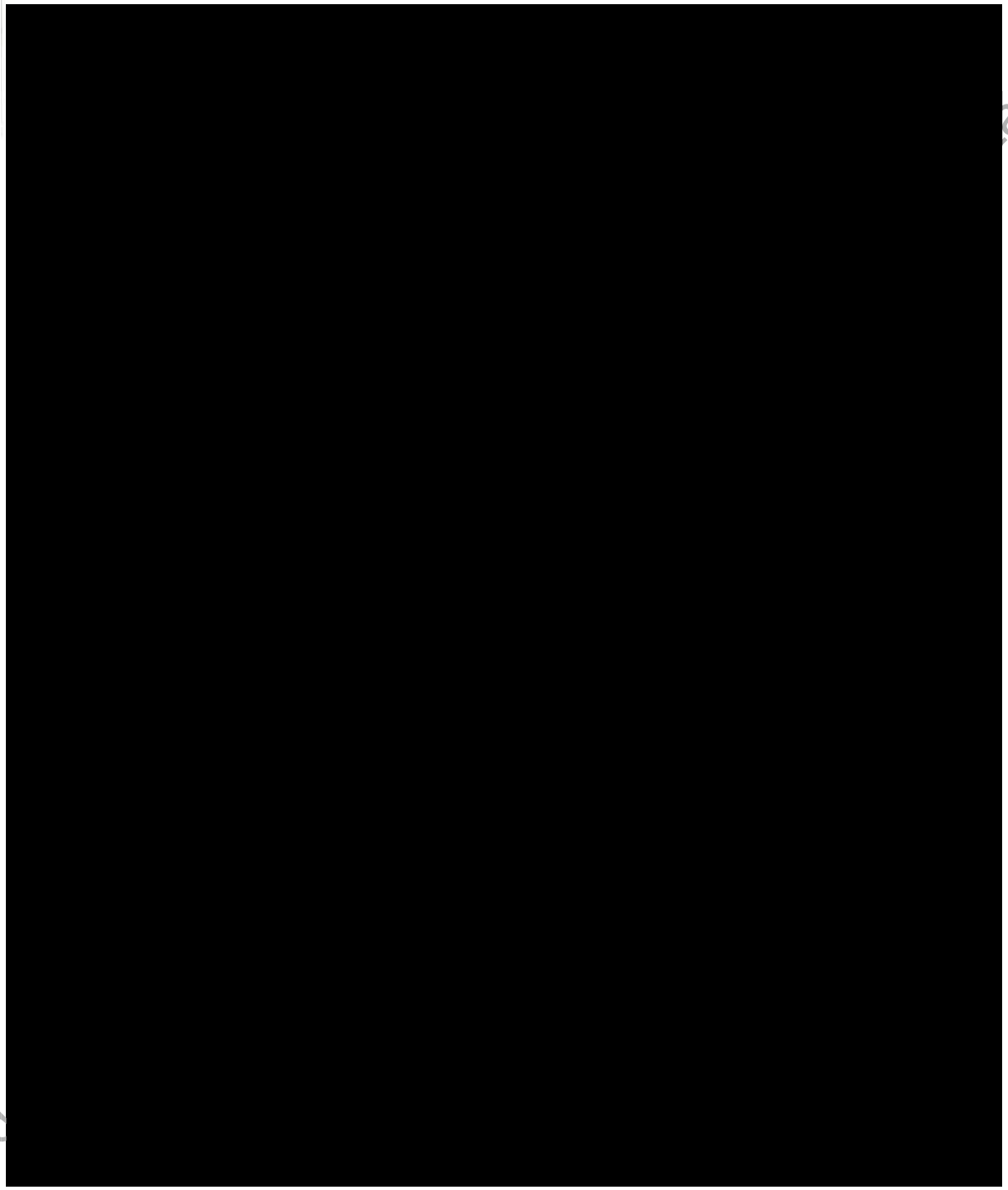

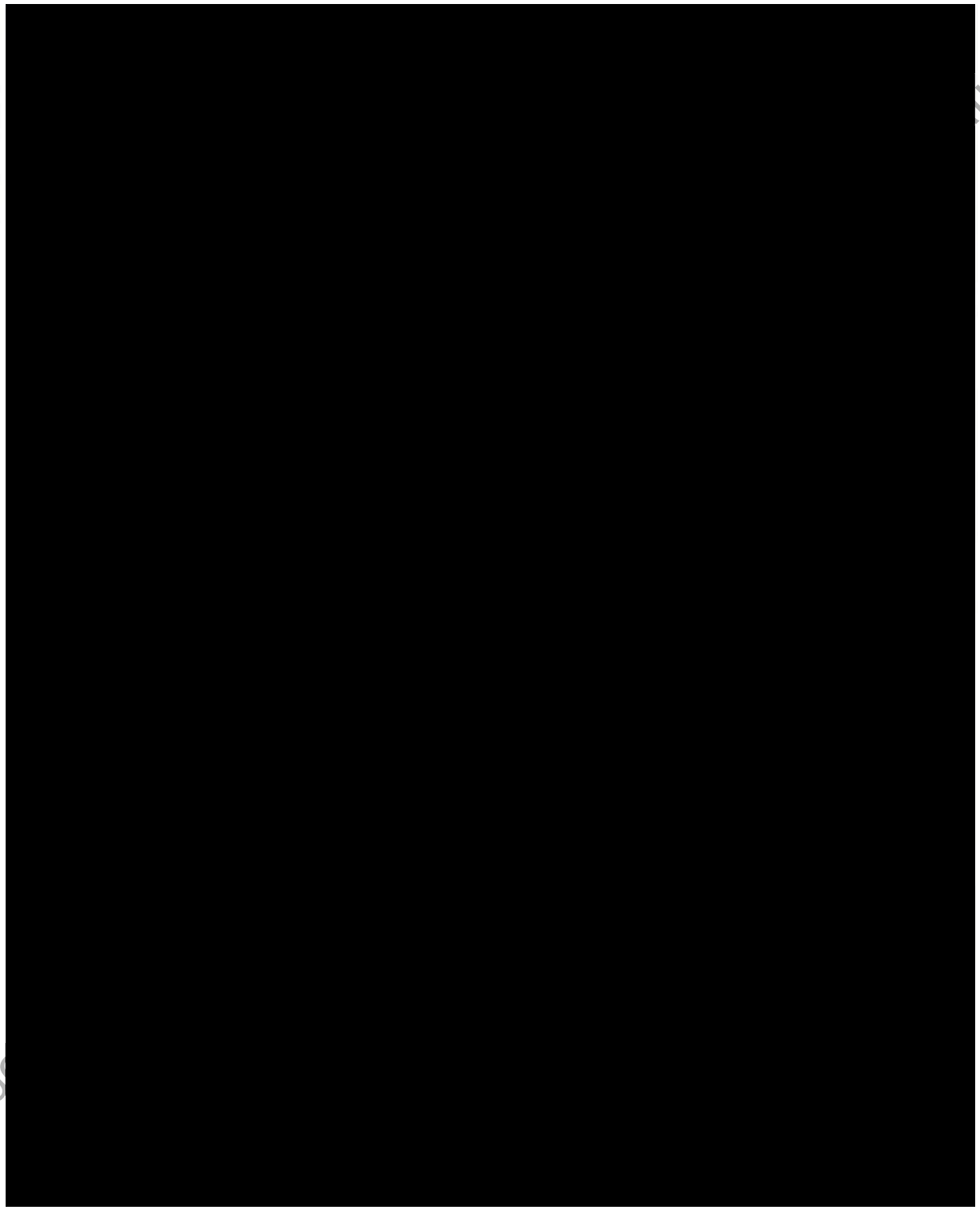

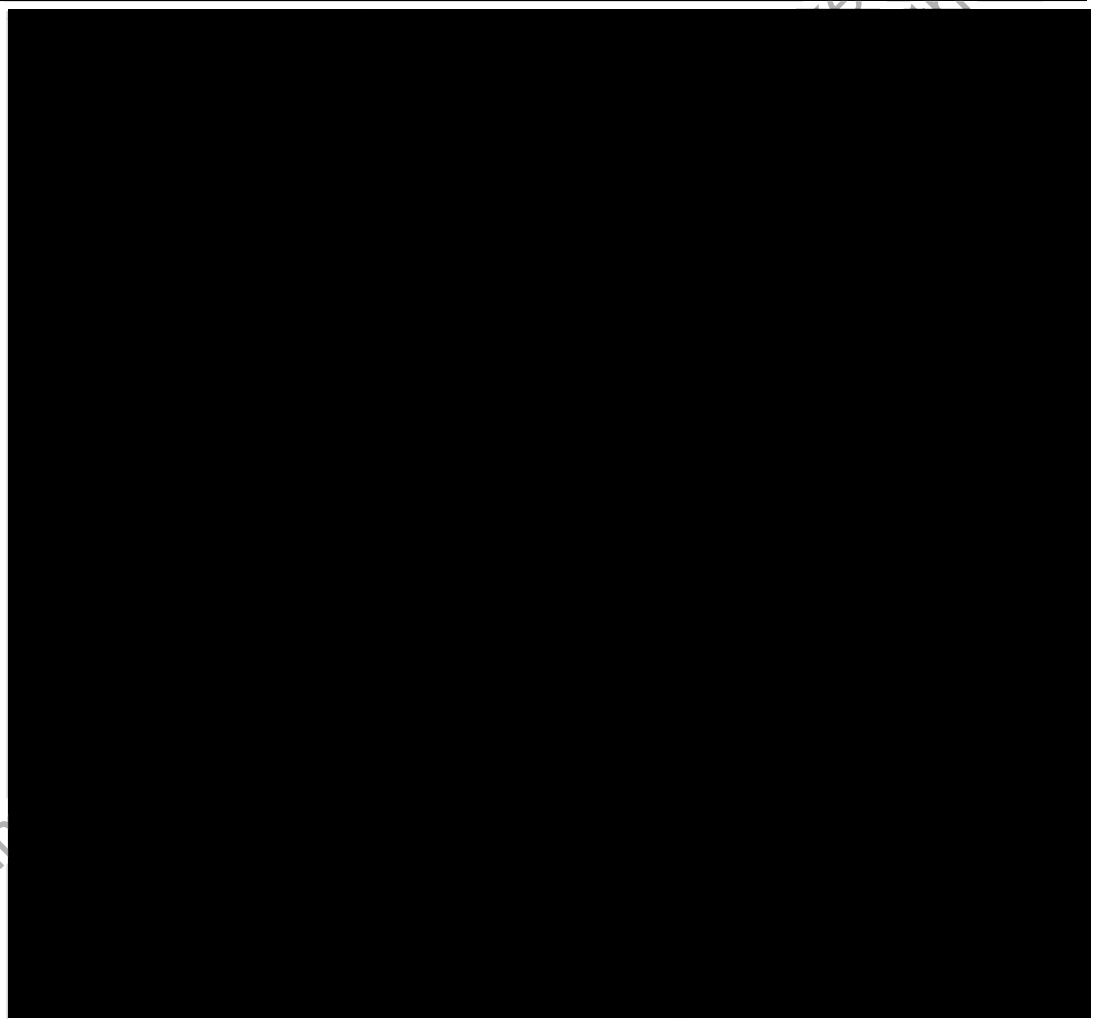

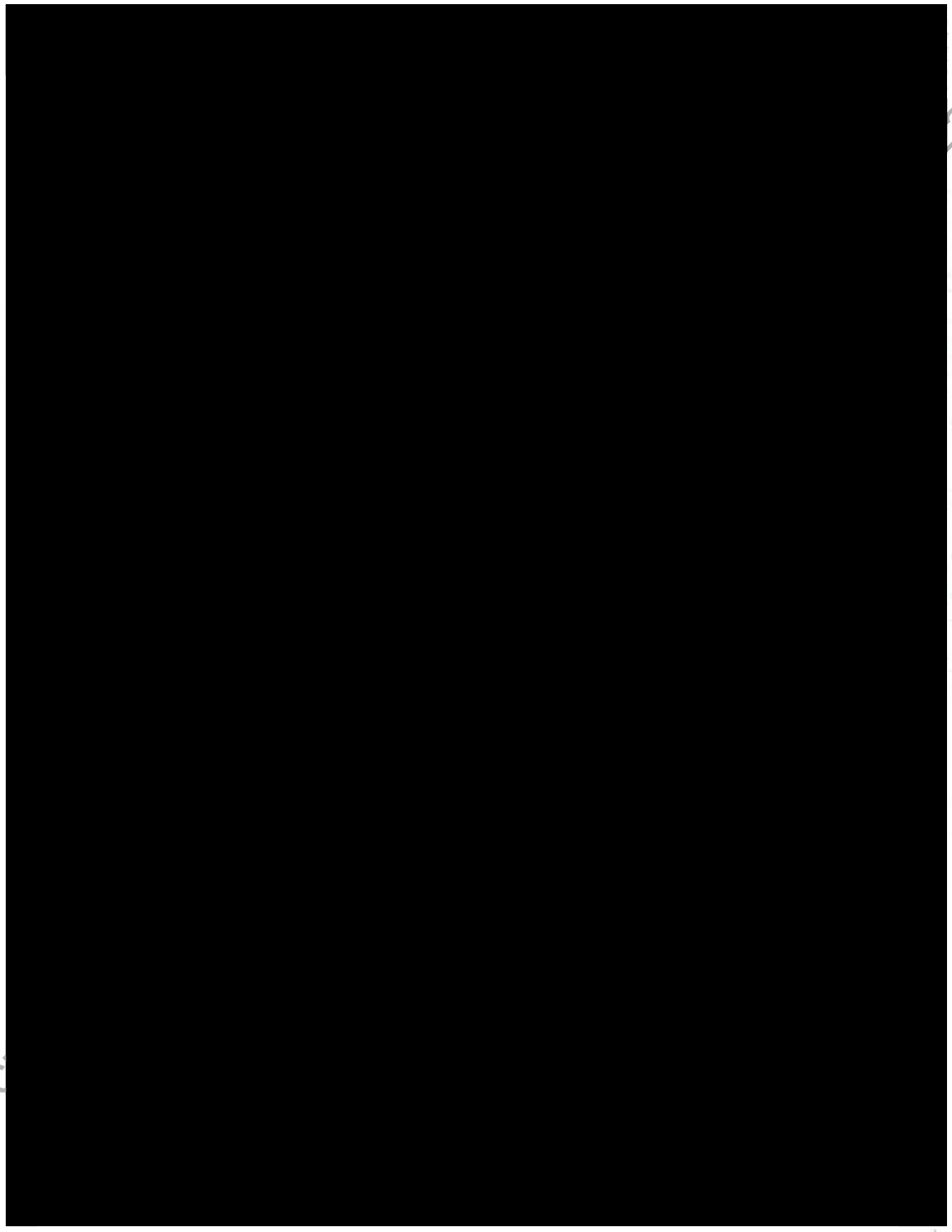

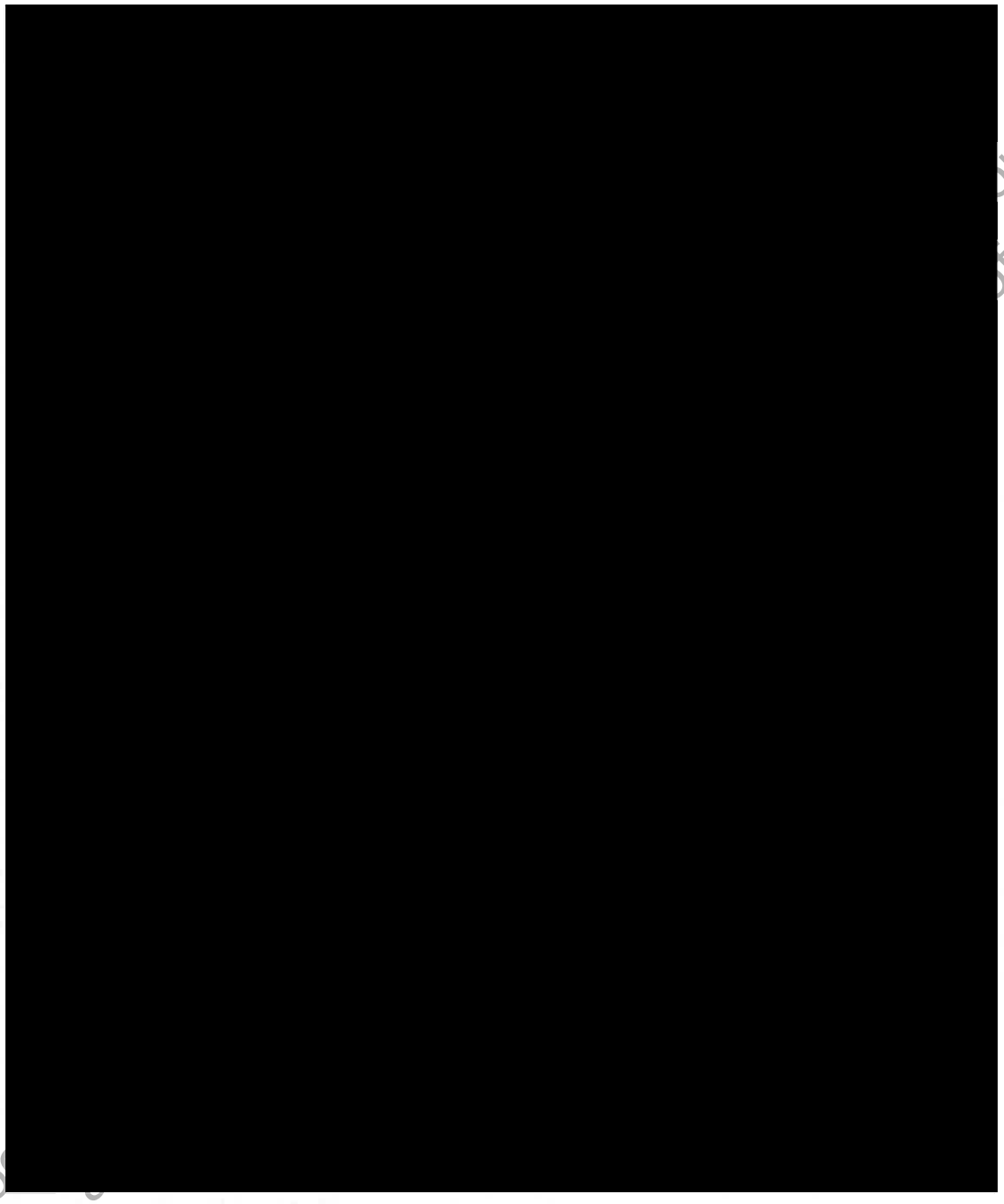

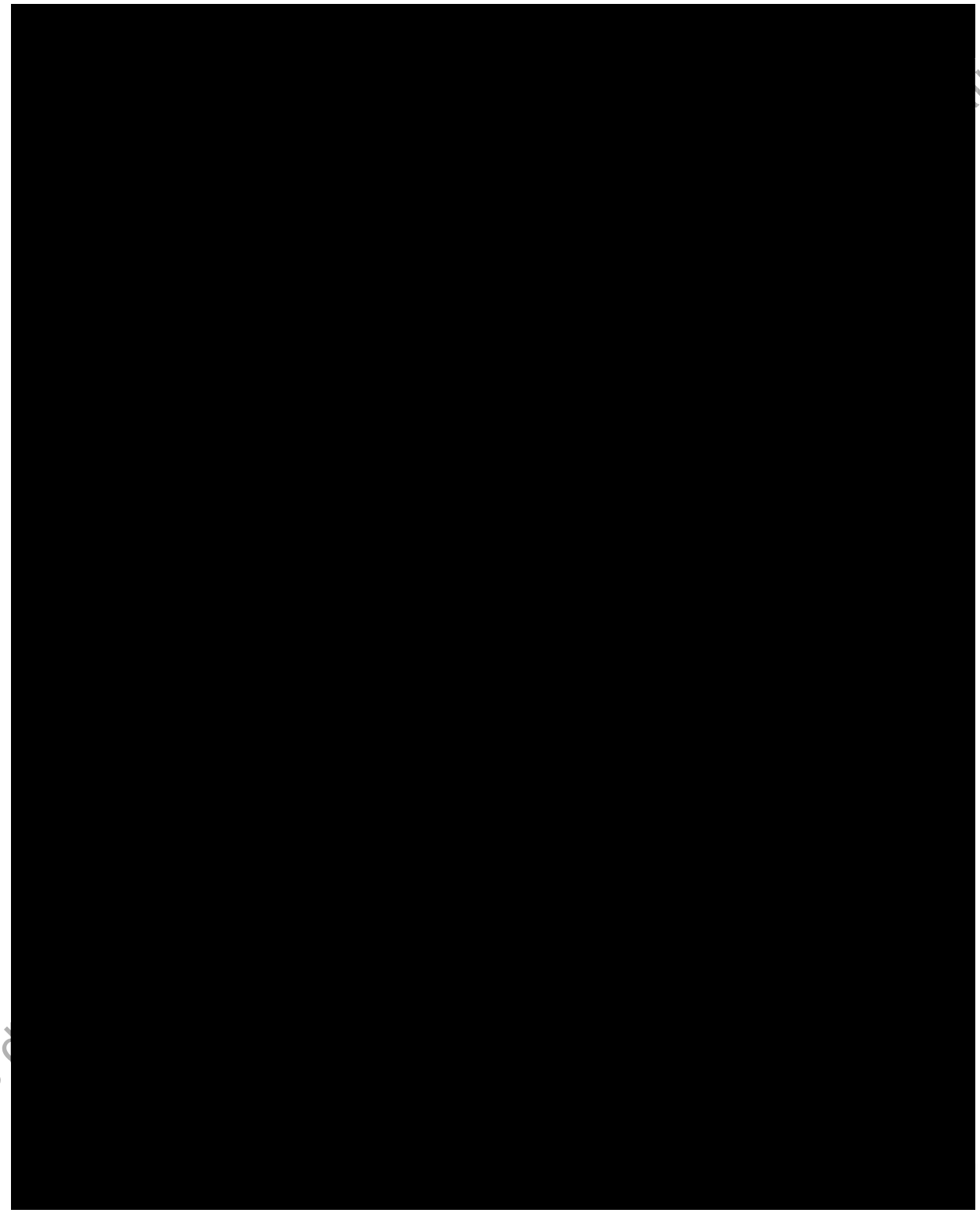

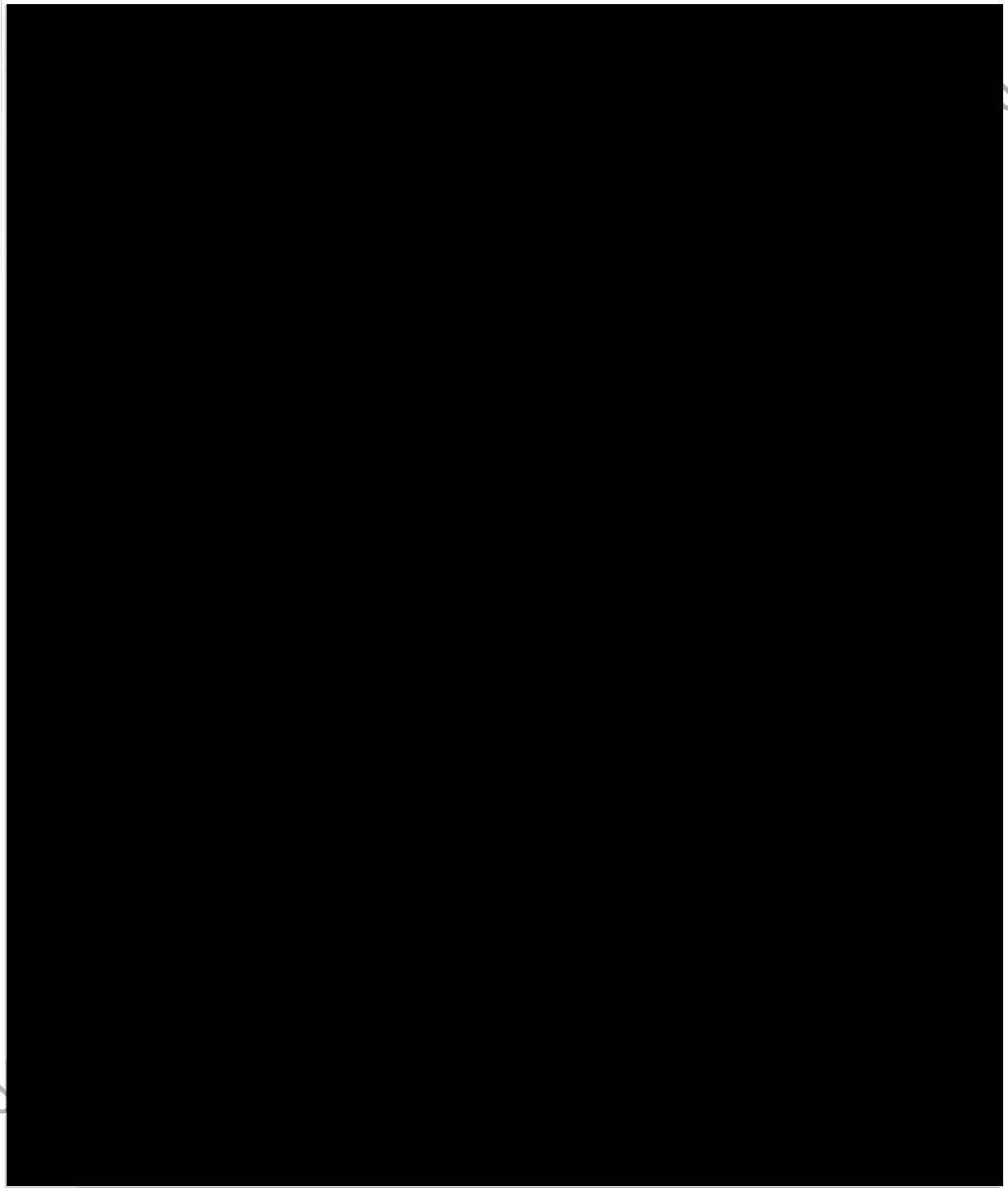

14.4 APPENDIX 4 – QUALITY OF LIFE IN CHILDHOOD EPILEPSY SCALE

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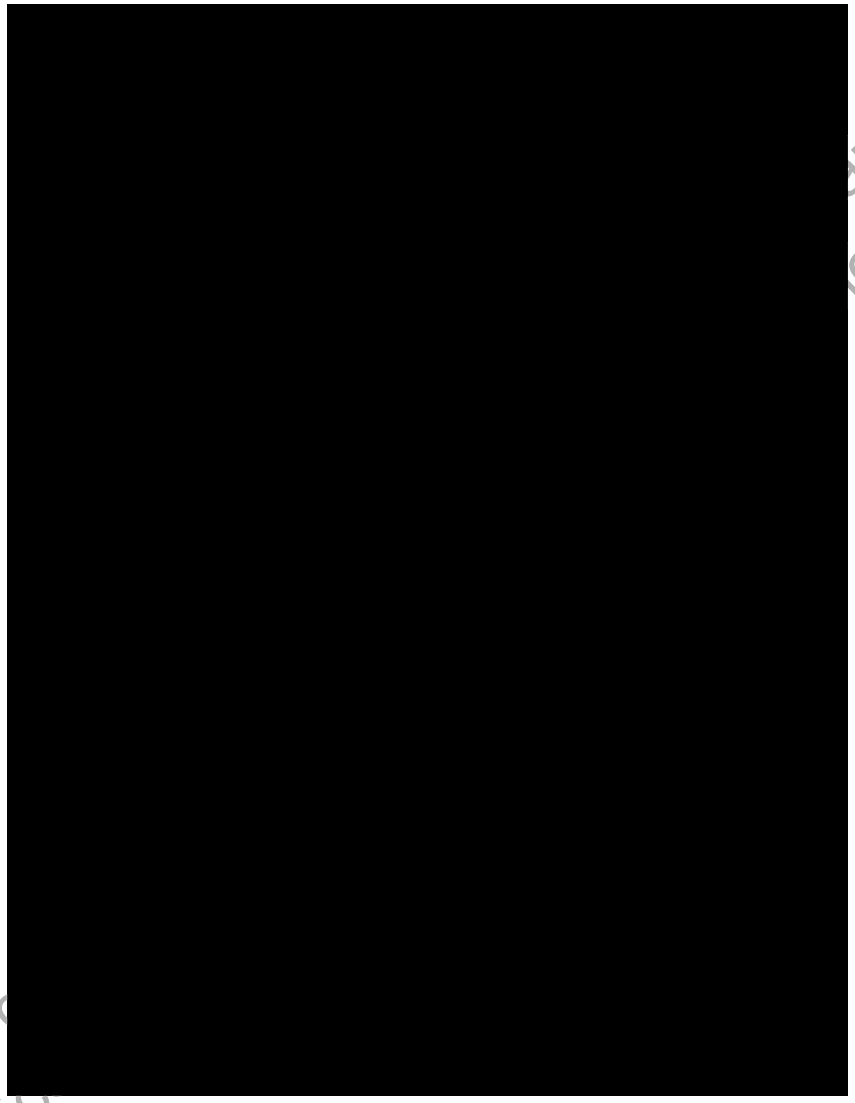

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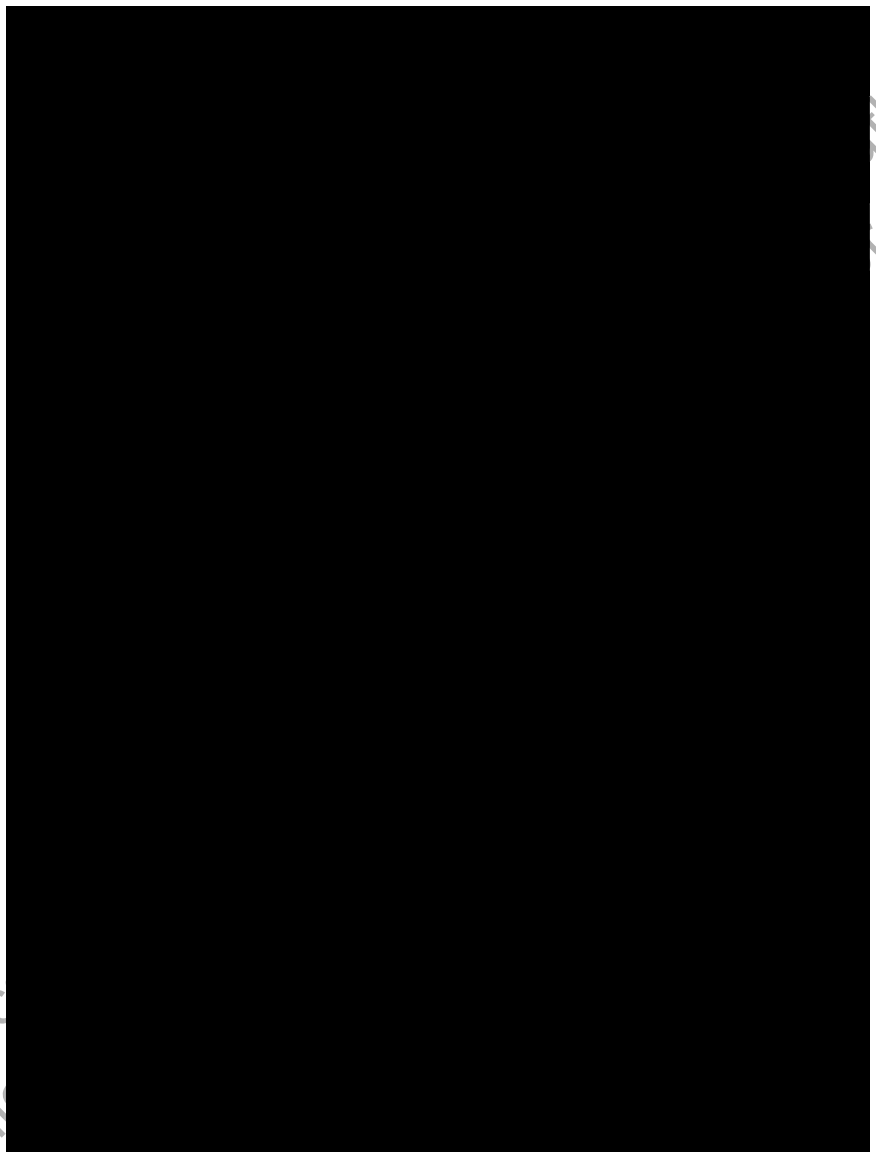

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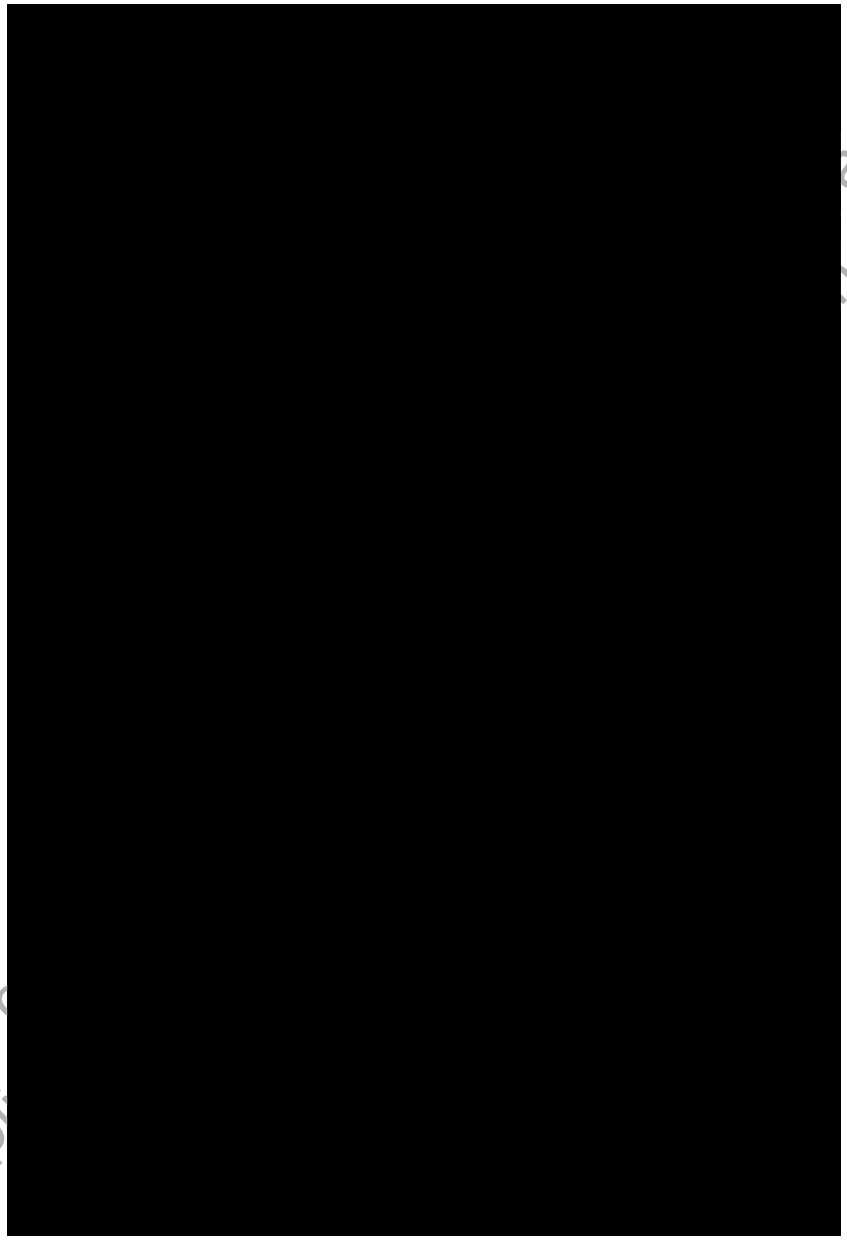

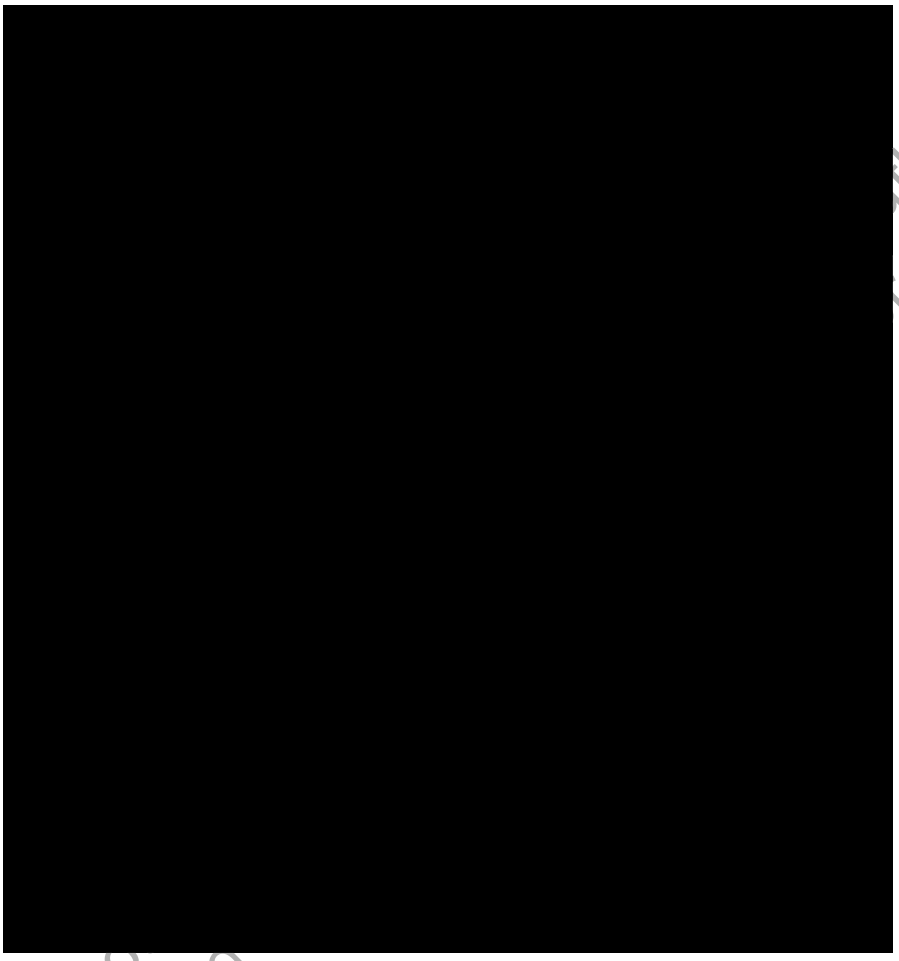

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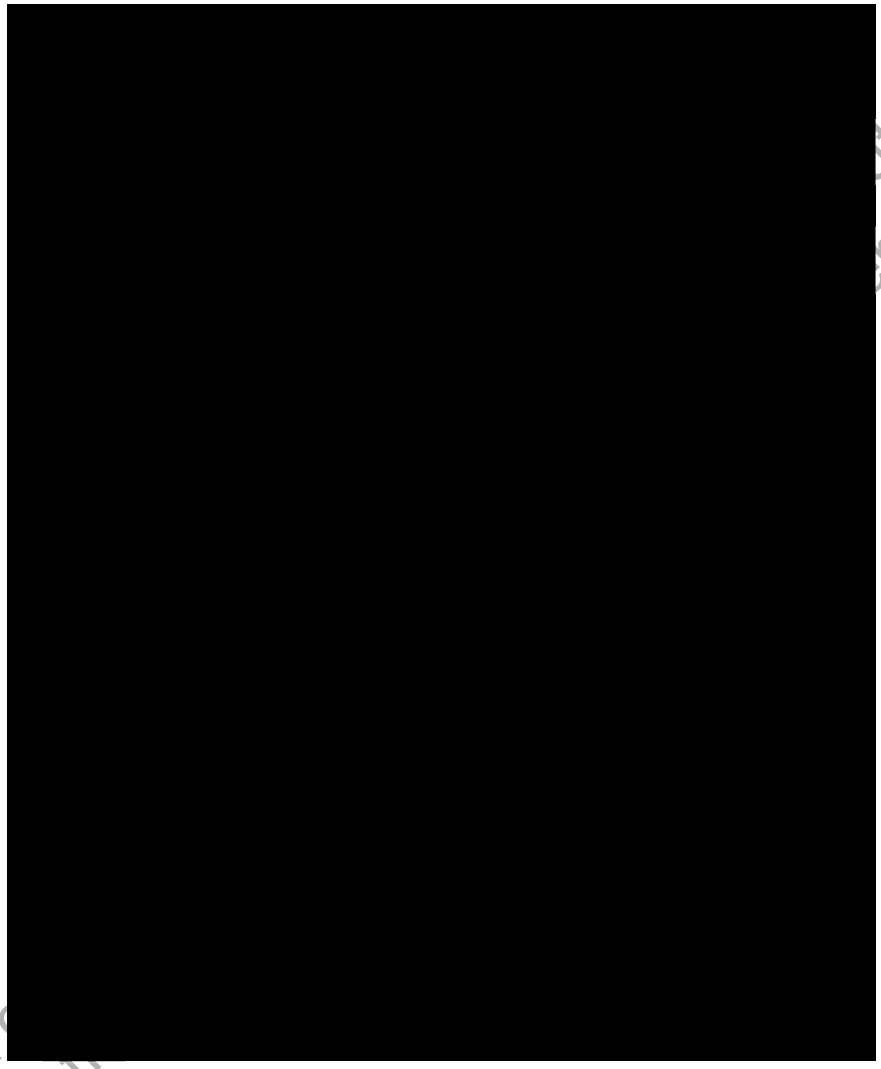

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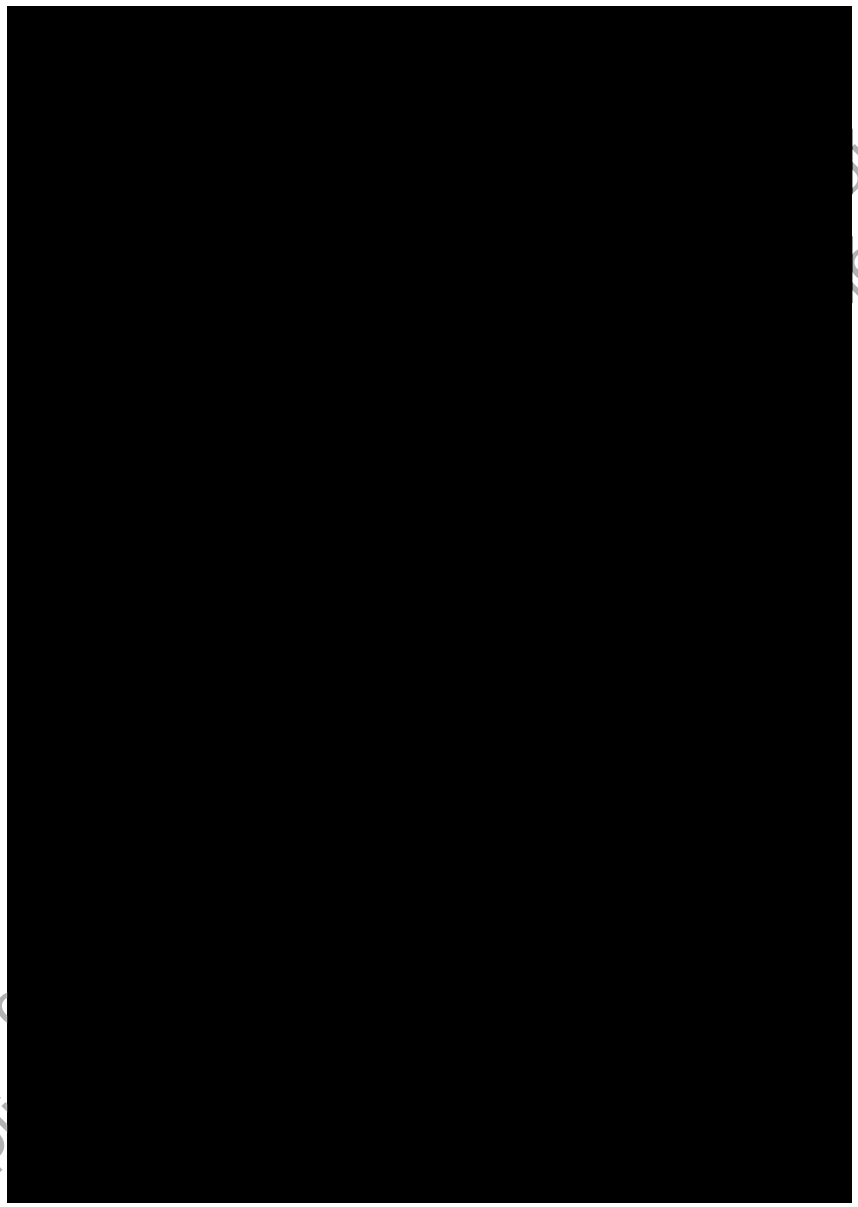

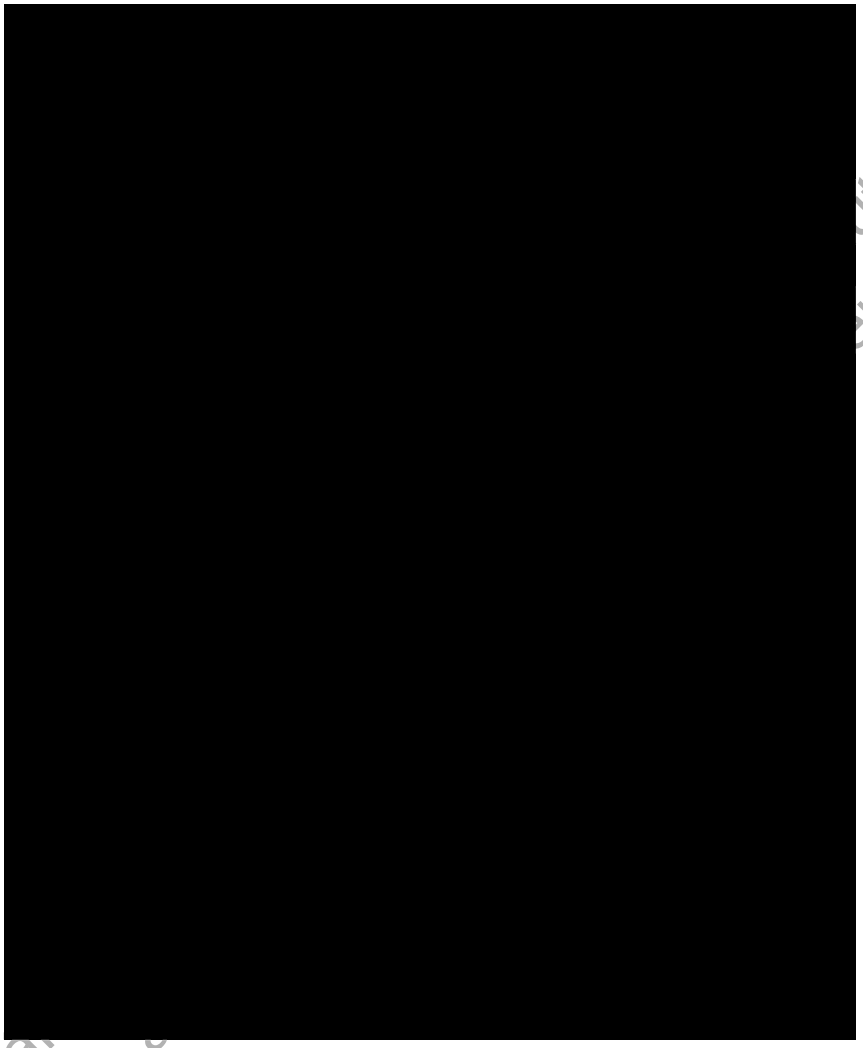

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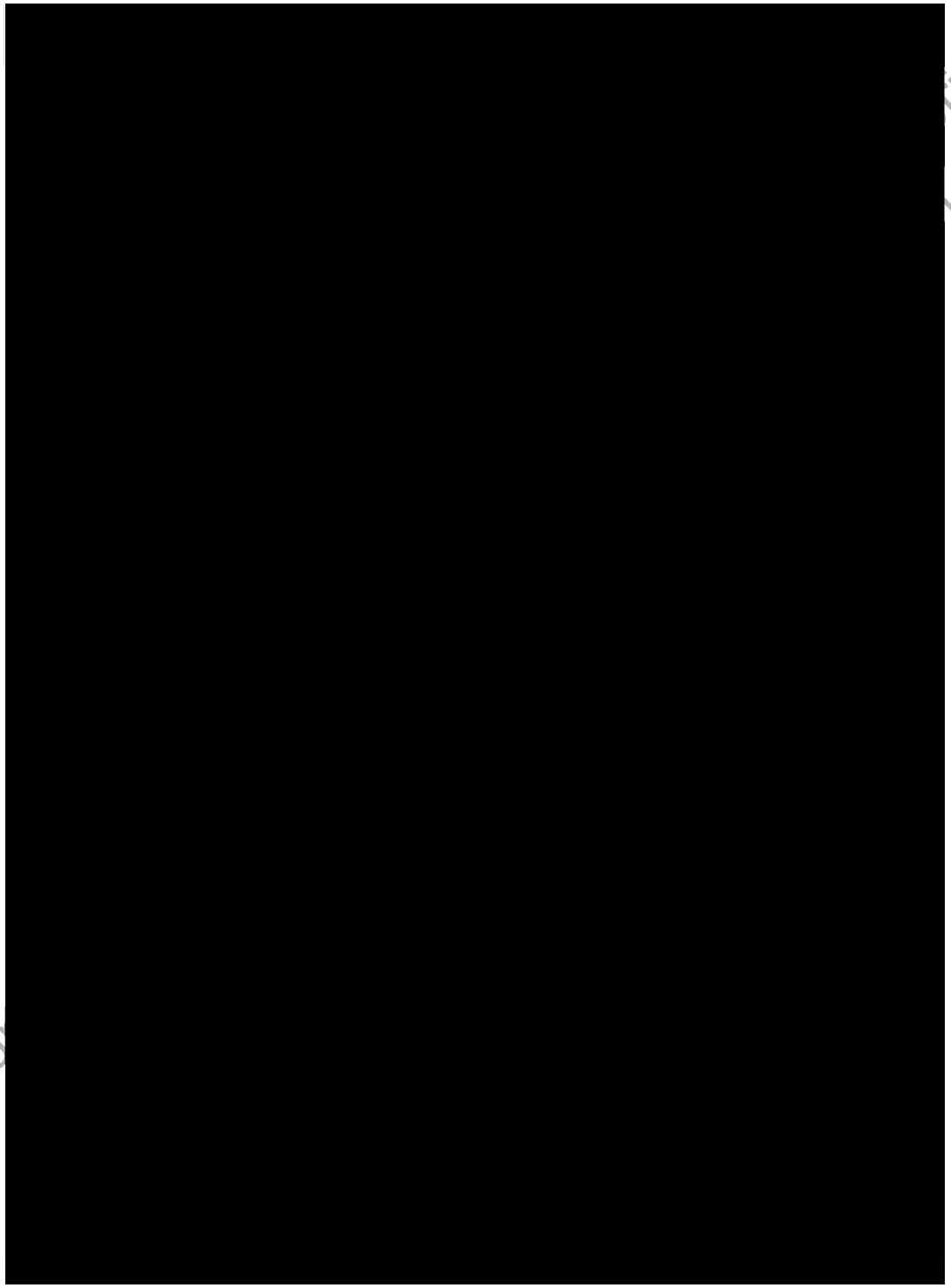
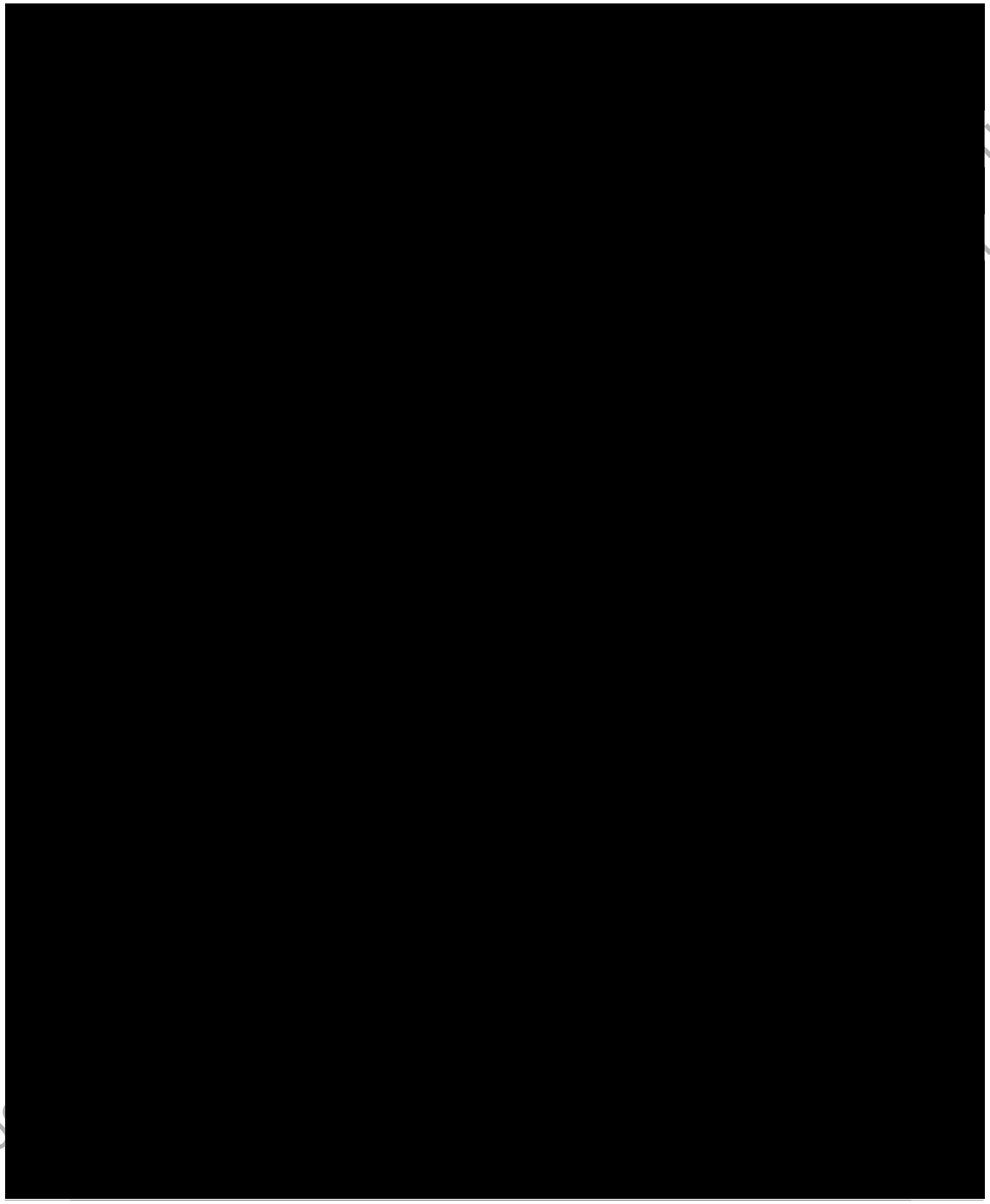
14.5 APPENDIX 5 – TANNER STAGING





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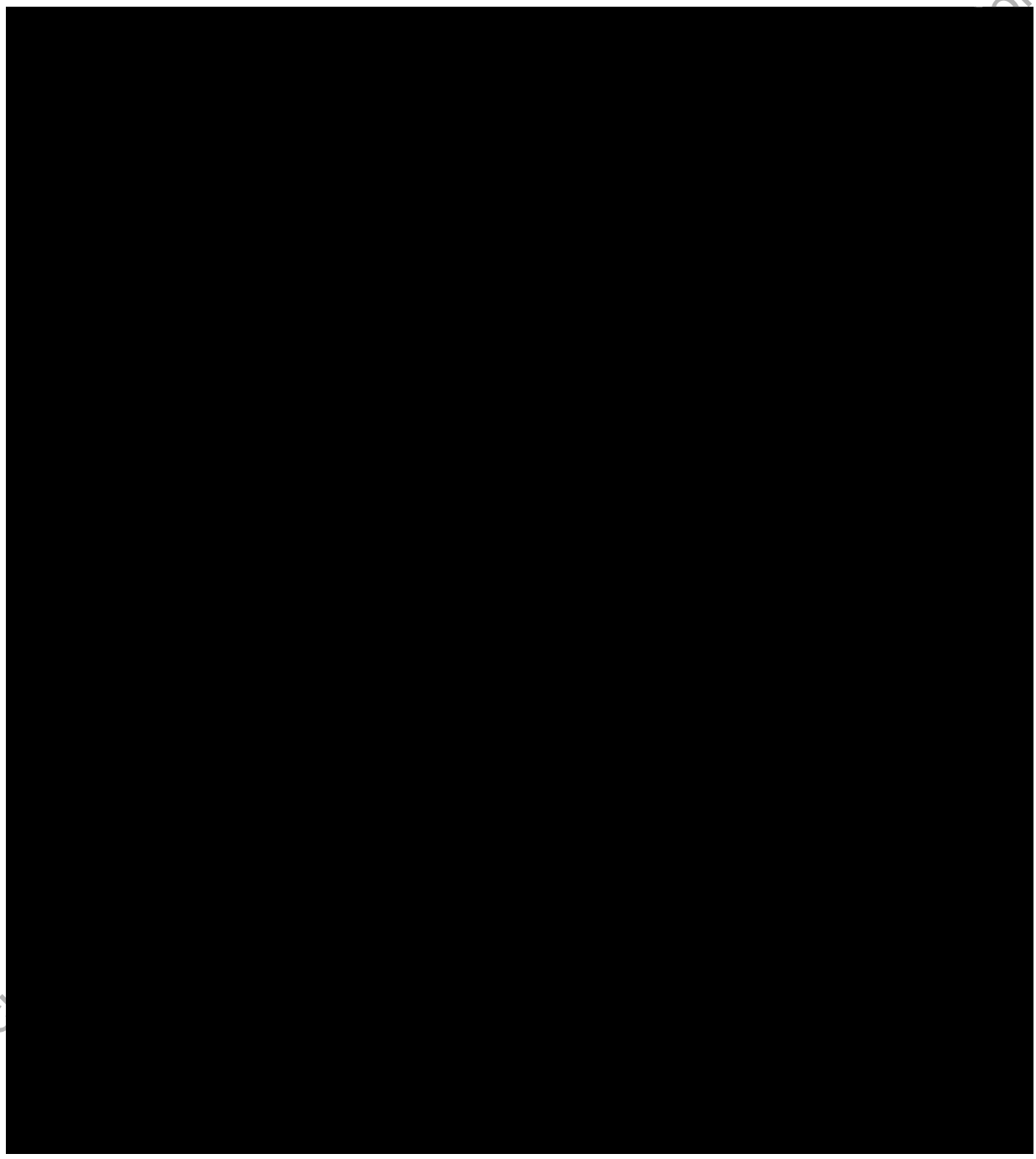

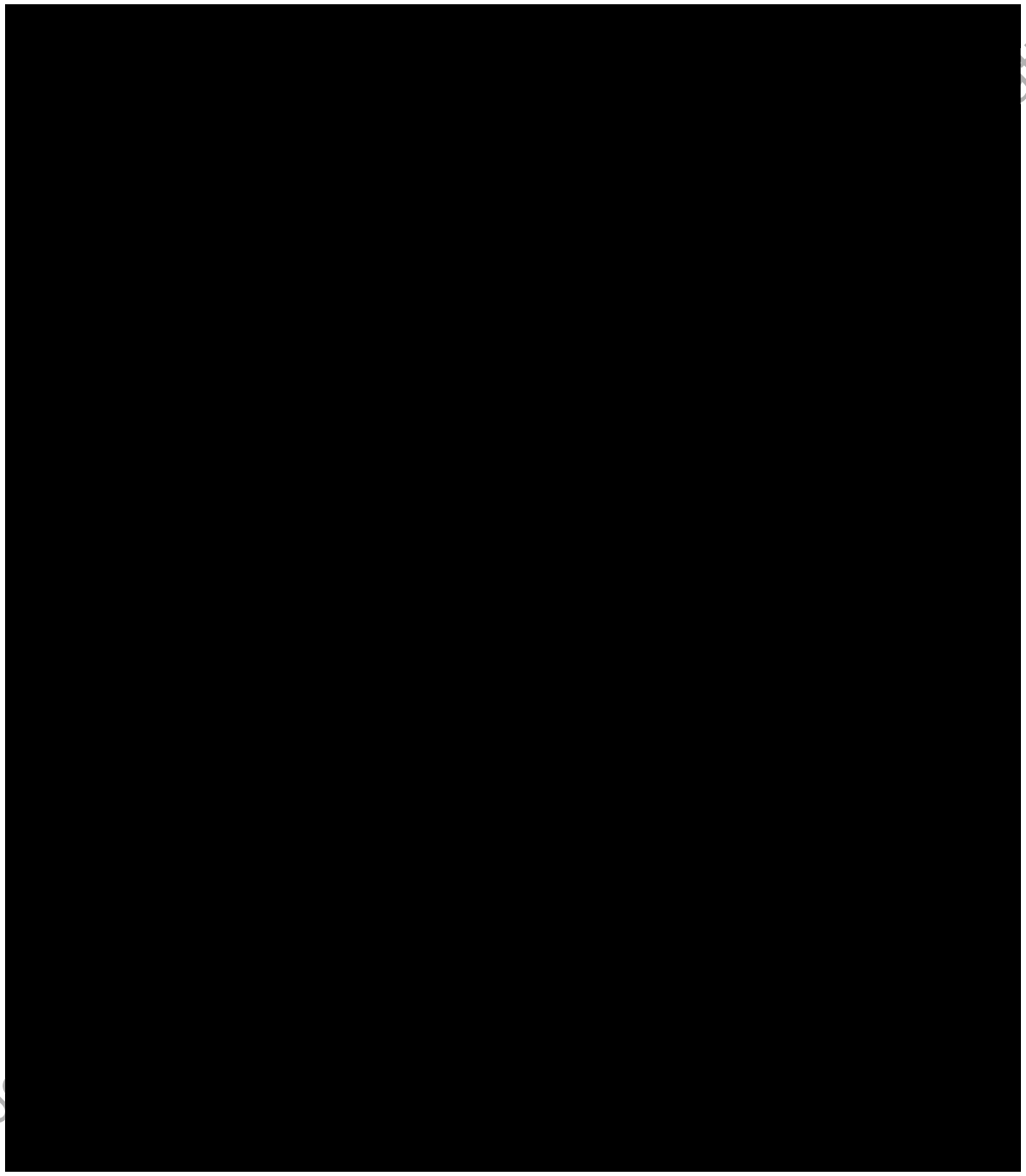

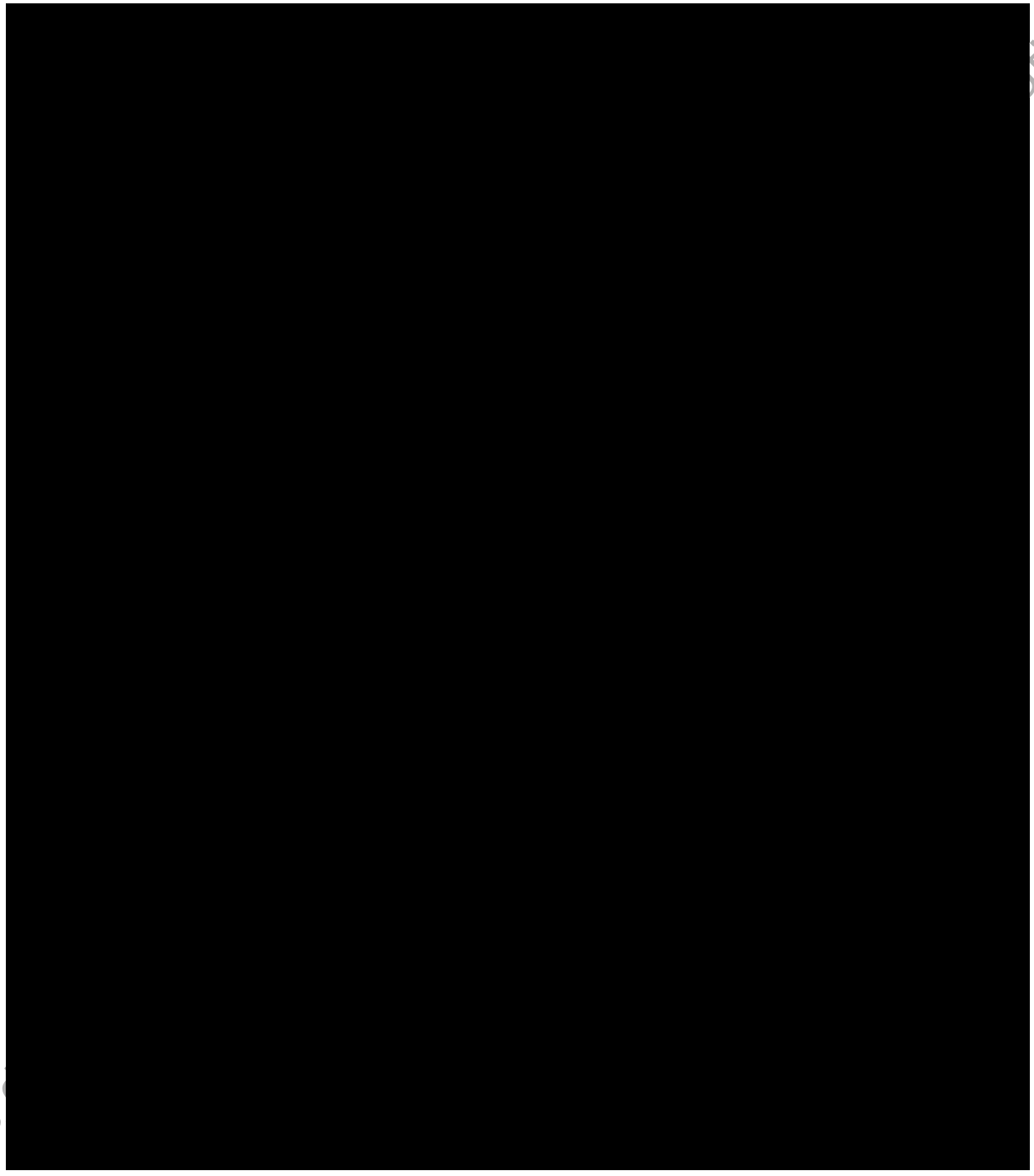

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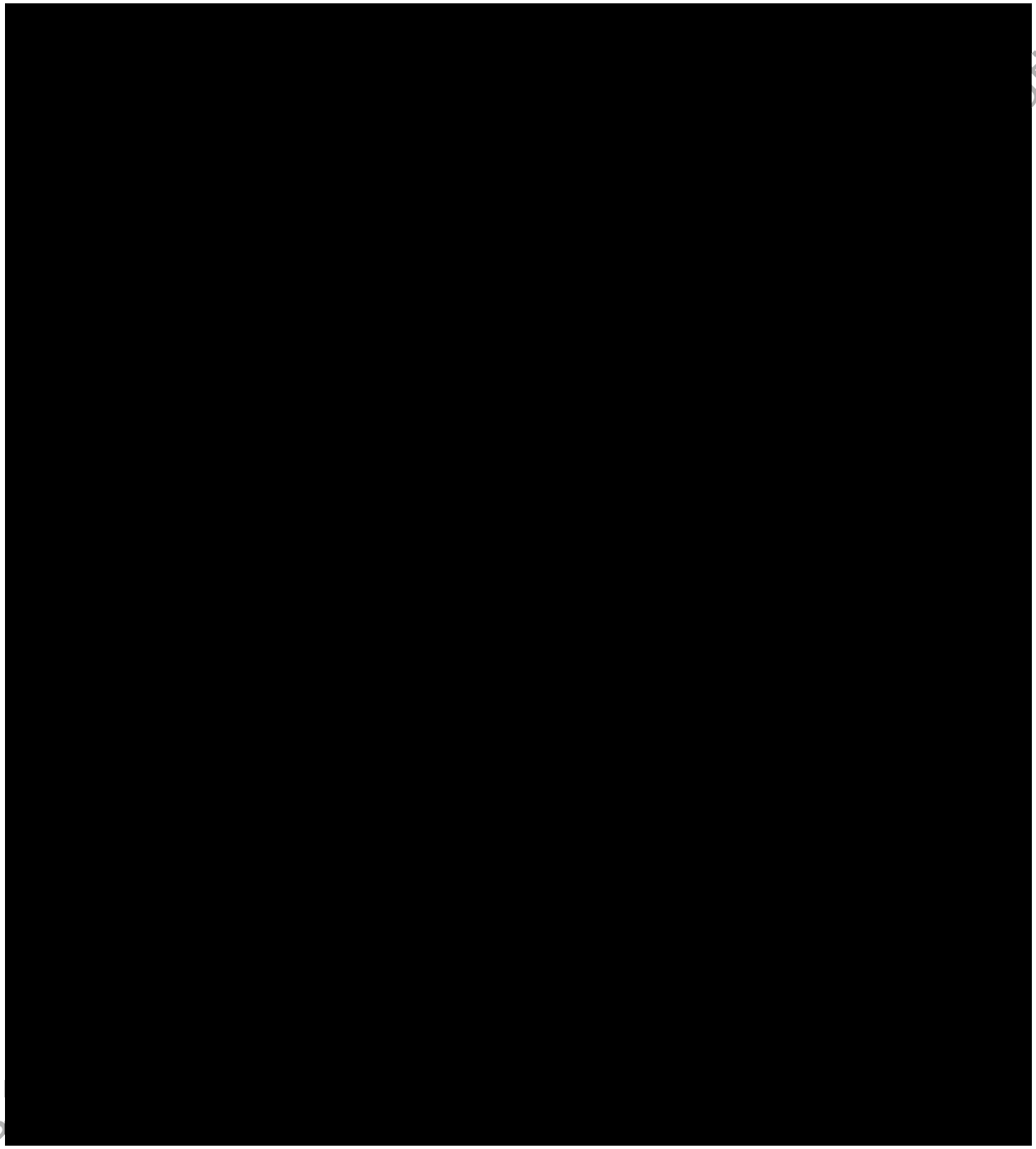

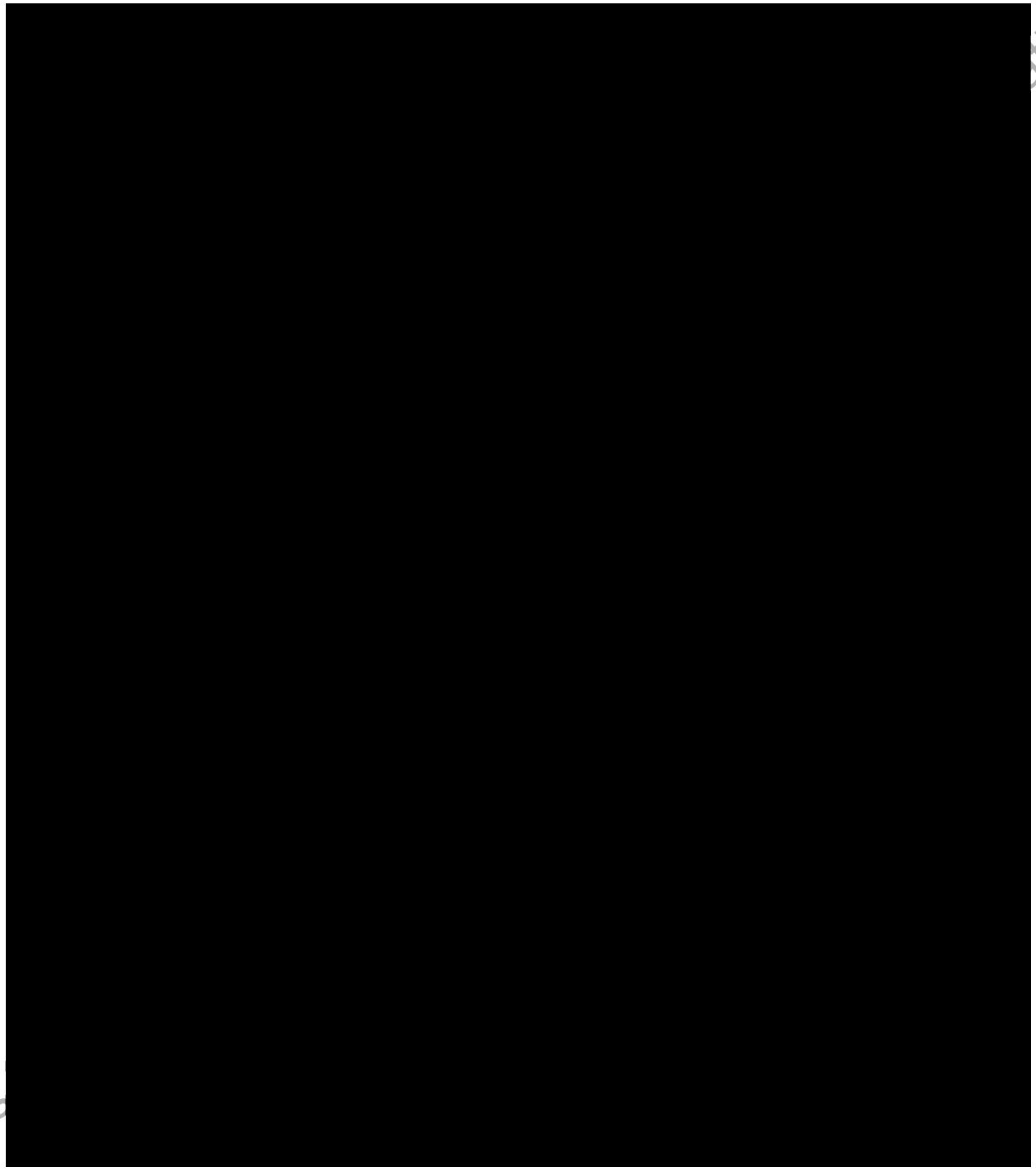

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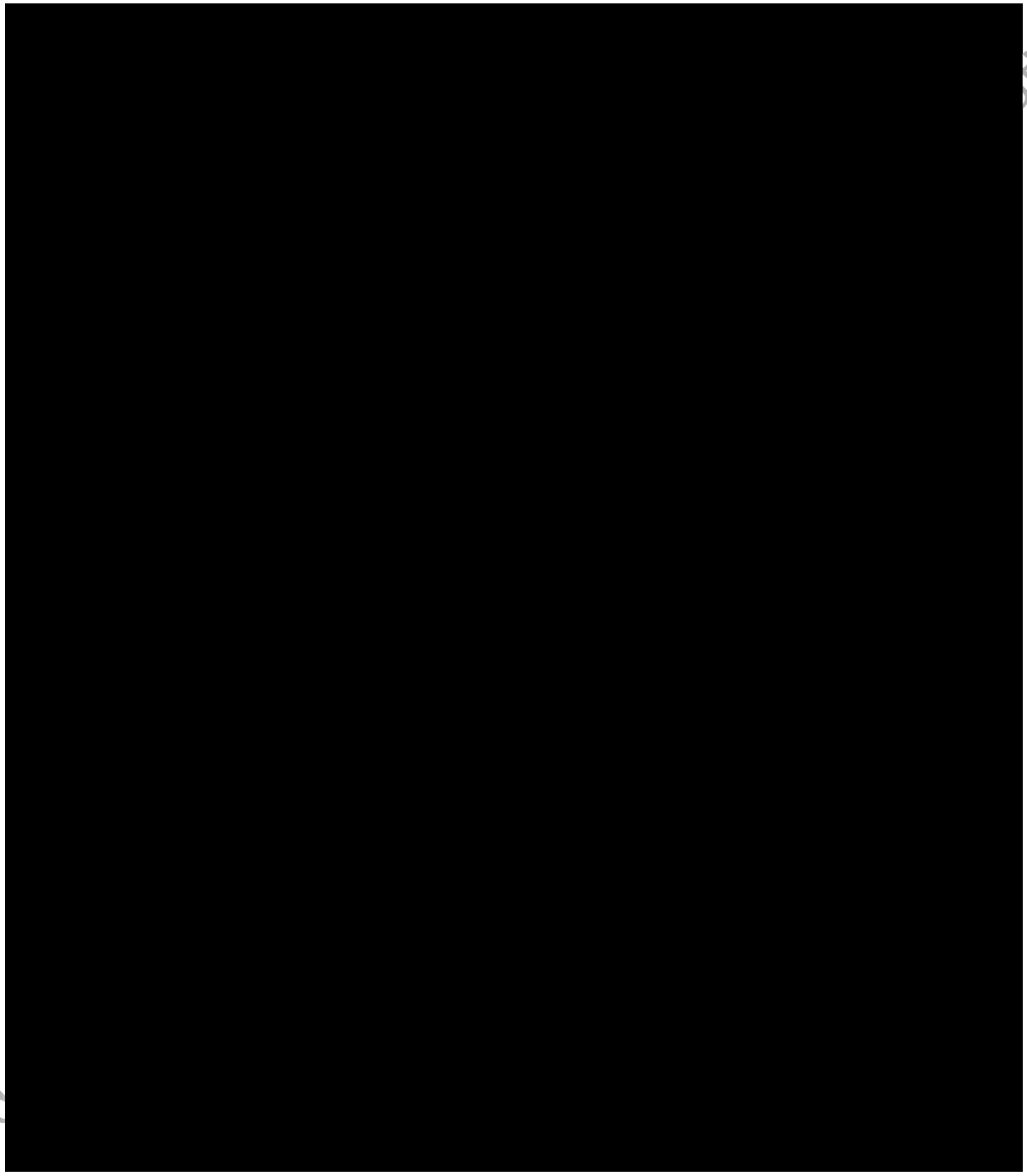

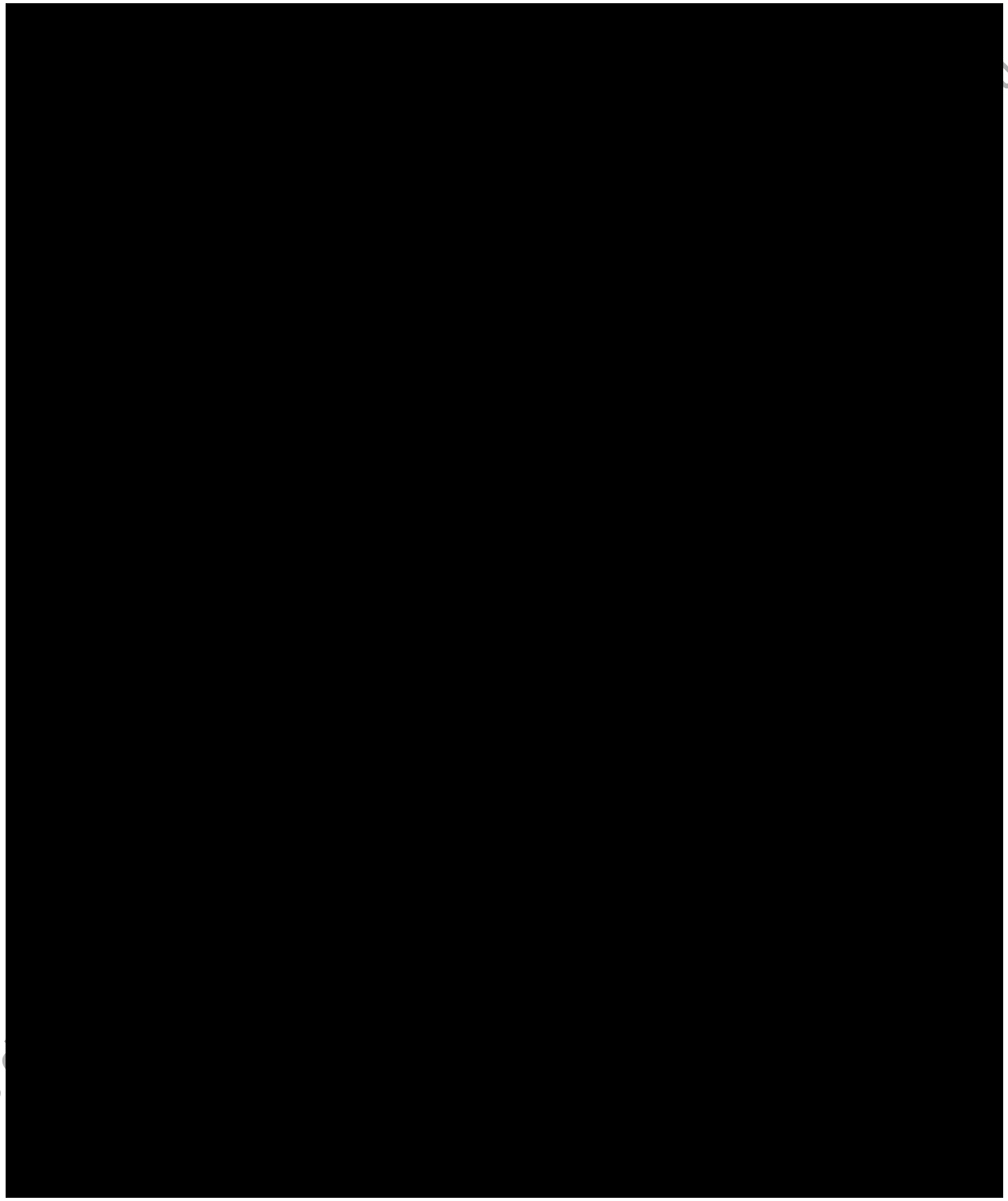

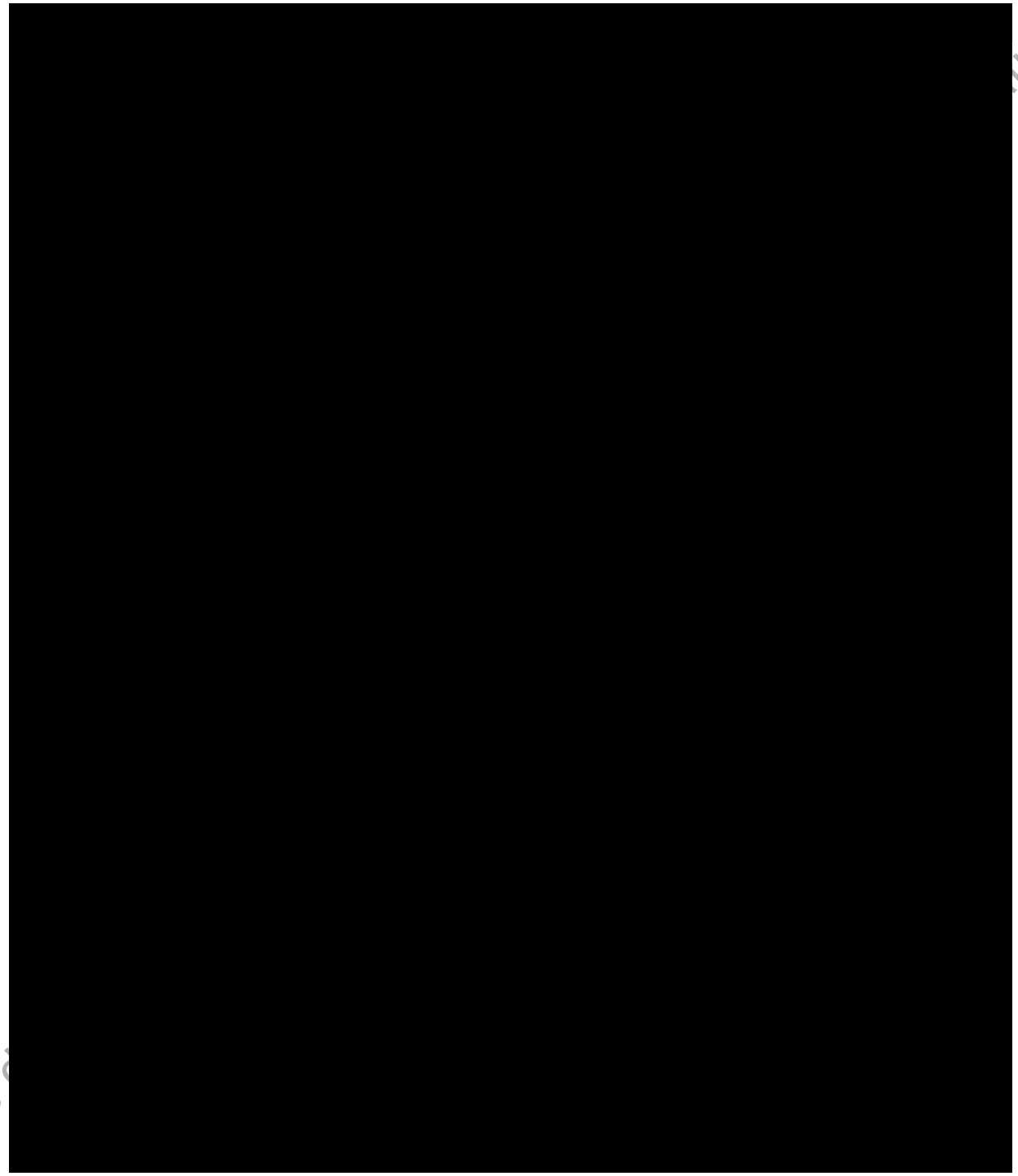

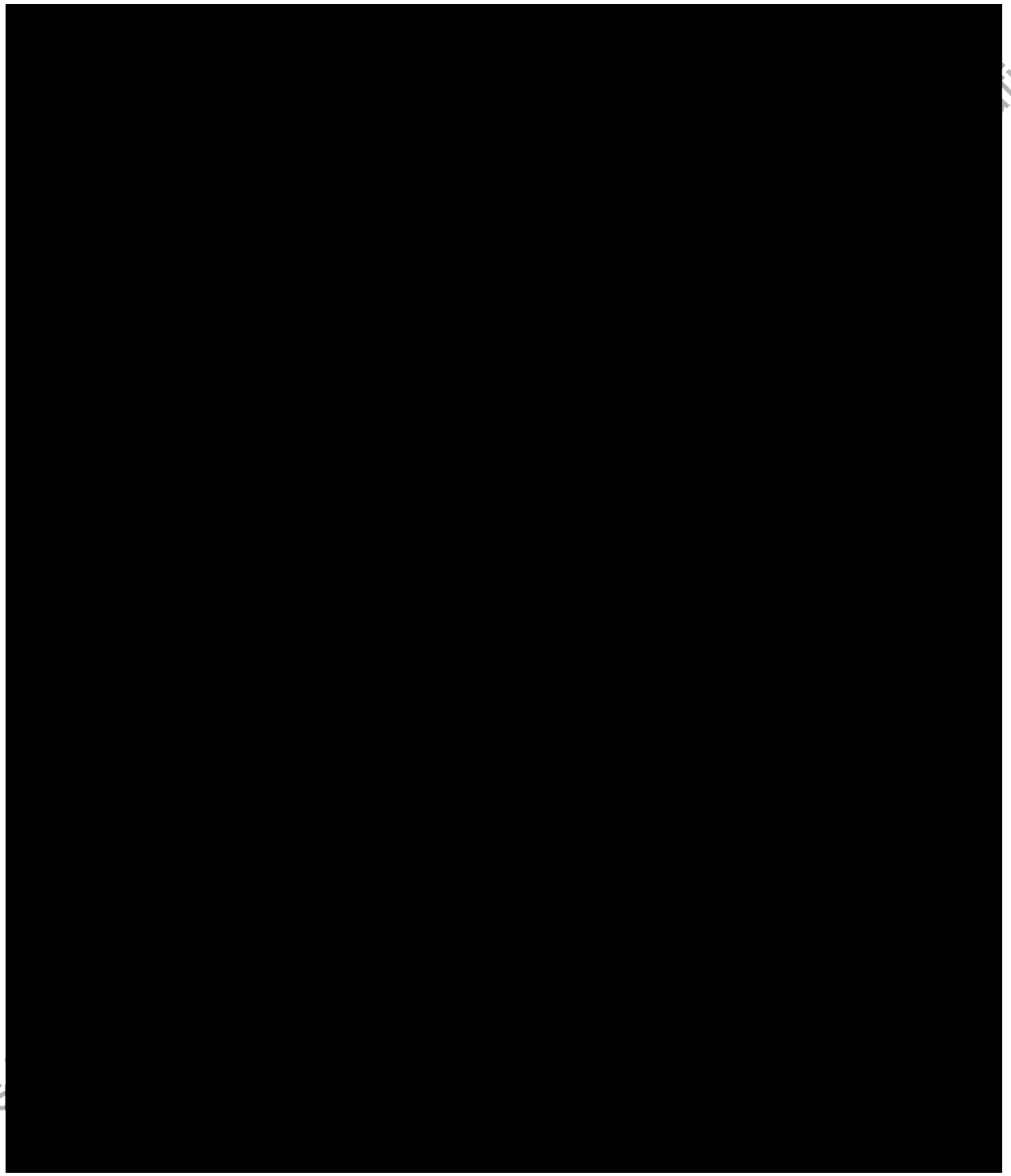

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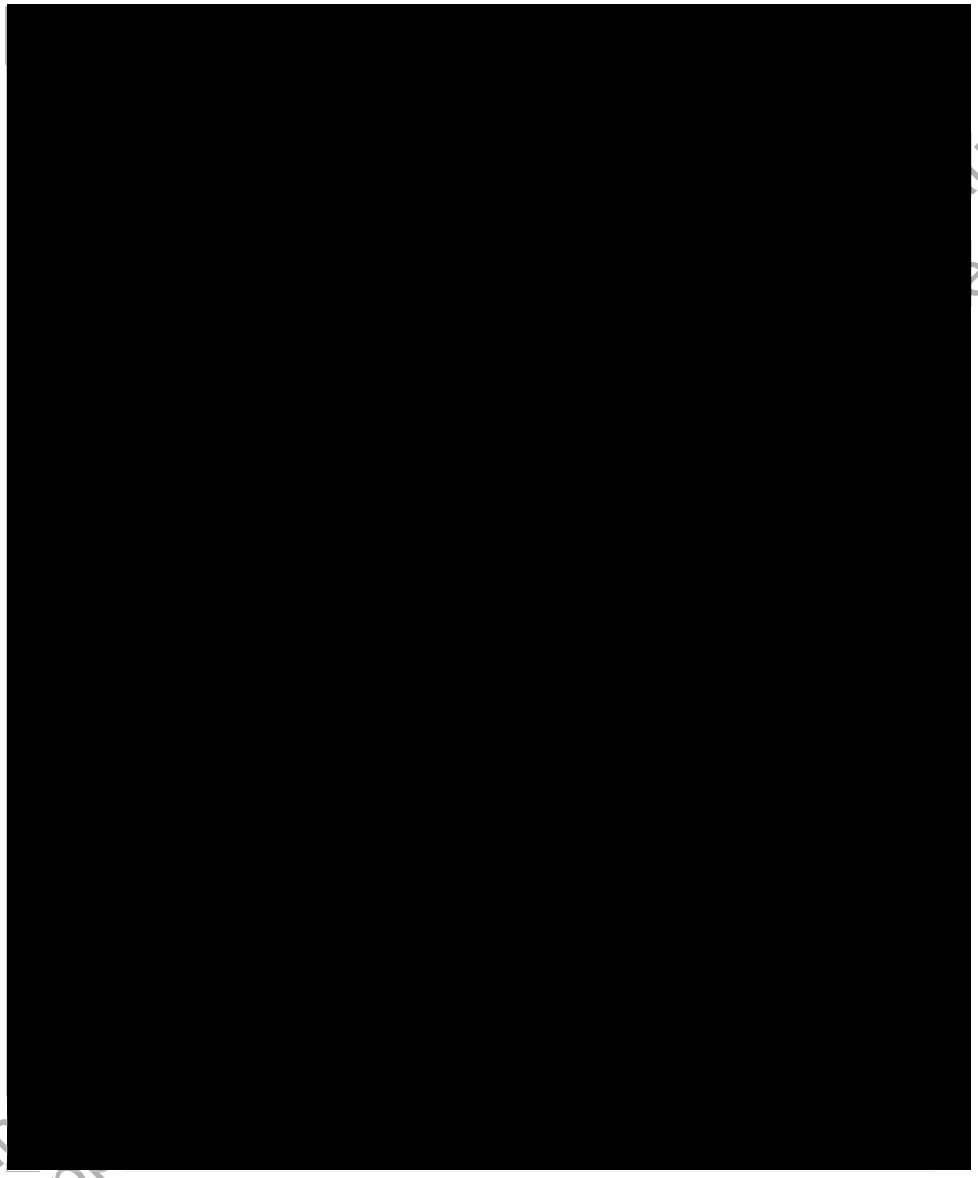

14.8 APPENDIX 8 – HOSPITAL ANXIETY AND DEPRESSION SCALE

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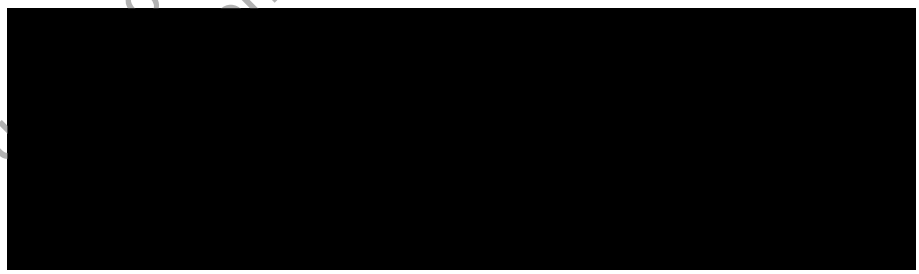

14.9 APPENDIX 9 – MAXIMUM ALLOWABLE BLOOD DRAW VOLUMES

Seattle Children's
HOSPITAL · RESEARCH · FOUNDATION

Maximum allowable blood draw volumes:

PATIENT'S WEIGHT		TOTAL VOLUME	MAXIMUM mL IN ONE BLOOD DRAW	MAXIMUM mL IN A 30-DAY PERIOD
Kg	lbs	mL	2.5% of total blood vol	5% of total blood vol
1	2.2	100	2.5	5
2	4.4	200	5	10
3	3.3	240	6	12
4	8.8	320	8	16
5	11	400	10	20
6	13.2	480	12	24
7	15.4	560	14	28
8	17.6	640	16	32
9	19.8	720	18	36
10	22	800	20	40
11 thru 15	24 thru 33	880-1200	22-30	44-60
16 thru 20	35 thru 44	1280-1600	32-40	64-80
21 thru 25	46 thru 55	1680-2000	42-50	64-100
26 thru 30	57 thru 66	2080-2400	52-60	104-120
31 thru 35	68 thru 77	2480-2800	62-70	124-140
36 thru 40	79 thru 88	2880-3200	72-80	144-160
41 thru 45	90 thru 99	3280-3600	82-90	164-180
46 thru 50	101 thru 110	3680-4000	92-100	184-200
51 thru 55	112 thru 121	4080-4400	102-110	204-220
56 thru 60	123 thru 132	4480-4800	112-120	224-240
61 thru 65	134 thru 143	4880-5200	122-130	244-260
66 thru 70	145 thru 154	5280-5600	132-140	264-280
71 thru 75	156 thru 165	5680-6000	142-150	284-300
76 thru 80	167 thru 176	6080-6400	152-160	304-360
81 thru 85	178 thru 187	6480-6800	162-170	324-340
86 thru 90	189 thru 198	6880-7200	172-180	344-360
91 thru 95	200 thru 209	7280-7600	182-190	364-380
96 thru 100	211 thru 220	7680-8000	192-200	384-400

Based on blood volume of:
1 to 2 kg 100 mL/kg (pre-term infant)
>2 kg 80 mL/kg (term infant - adult)
This information is similar to that used by the Committee on Clinical Investigations at Children's Hospital in Los Angeles, and at Baylor College of Medicine in Dallas, TX.

Adapted by [redacted] August 2001
Children's Hospital and Regional Medical Center Laboratory
Seattle, WA

Seattle Children's
HOSPITAL · RESEARCH · FOUNDATION

Maximum allowable blood draw volumes:

PATIENT'S WEIGHT		TOTAL VOLUME	MAXIMUM mL IN ONE BLOOD DRAW	MAXIMUM mL IN A 30-DAY PERIOD
Kg	lbs	mL	2.5% of total blood vol	5% of total blood vol
1	2.2	100	2.5	5
2	4.4	200	5	10
3	3.3	240	6	12
4	8.8	320	8	16
5	11	400	10	20
6	13.2	480	12	24
7	15.4	560	14	28
8	17.6	640	16	32
9	19.8	720	18	36
10	22	800	20	40
11 thru 15	24 thru 33	880-1200	22-30	44-60
16 thru 20	35 thru 44	1280-1600	32-40	64-80
21 thru 25	46 thru 55	1680-2000	42-50	64-100
26 thru 30	57 thru 66	2080-2400	52-60	104-120
31 thru 35	68 thru 77	2480-2800	62-70	124-140
36 thru 40	79 thru 88	2880-3200	72-80	144-160
41 thru 45	90 thru 99	3280-3600	82-90	164-180
46 thru 50	101 thru 110	3680-4000	92-100	184-200
51 thru 55	112 thru 121	4080-4400	102-110	204-220
56 thru 60	123 thru 132	4480-4800	112-120	224-240
61 thru 65	134 thru 143	4880-5200	122-130	244-260
66 thru 70	145 thru 154	5280-5600	132-140	264-280
71 thru 75	156 thru 165	5680-6000	142-150	284-300
76 thru 80	167 thru 176	6080-6400	152-160	304-360
81 thru 85	178 thru 187	6480-6800	162-170	324-340
86 thru 90	189 thru 198	6880-7200	172-180	344-360
91 thru 95	200 thru 209	7280-7600	182-190	364-380
96 thru 100	211 thru 220	7680-8000	192-200	384-400

Based on blood volume of:
1 to 2 kg 100 mL/kg (pre-term infant)
>2 kg 80 mL/kg (term infant - adult)
This information is similar to that used by the Committee on Clinical Investigations at Children's Hospital in Los Angeles, and at Baylor College of Medicine in Dallas, TX.

Adapted by [redacted] August 2001
Children's Hospital and Regional Medical Center Laboratory
Seattle, WA

14.10 APPENDIX 10 – KAROLINSKA SLEEPINESS SCALE

14.11 APPENDIX 11 - 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 15, remote visits via telephone or video are acceptable when subjects are unable to travel to the site for in-person visits due to COVID-19 circumstances. The following information should be collected and recorded in the source documentation and in the EDC where applicable. Log pages (e.g. AEs, concomitant medication changes) will be entered normally as they are not associated with specific visits; assessment forms located within a particular visit page will also be entered normally, however, queries will be fired to capture specific information explaining the basis for missing or alternatively collected (ie. remote) data. Detailed instruction for EDC entry may be found in the CRF Completion Guidelines (CCGs).

- Date and time of the telephone/video visit
- Any changes in health status
- AEs/SAE assessment
- Concomitant medication query
- Review seizure and medication diary with parent/caregiver for compliance and any abnormalities in seizure activity
- Scales and Questionnaires, when applicable and if feasible
  - C-SSRS
  - CGI-I (by Investigator)

- Tanner Staging

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

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

EOS/ET for subjects tapering off ZX008:

For the EOS/ET visit (Visit 16) and Post-Dosing Follow-up visit (Visits 17-19), 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.

EOS/ET for subjects transitioning to Commercial drug:

For the EOS/ET visit (Visit 16) and Post-Dosing Follow-up visit (Visit 17), 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 an ECHO within 3-6 months before starting commercial drug and will have follow-up ECHOs within the required timeframe while on commercial drug.

EOS/ET for subjects transitioning to another extension study:

For subjects transitioning into another ZX008 extension study that are unable to attend the EOS/ET visit due to restrictions to traveling to the study site, delays in the start-up of the extension study, or other COVID-related delays, the EOS/ET visit may be delayed until an in-person visit is conducted. Therefore, subjects may remain on study for longer than the planned duration of participation. If the delay is over 6 weeks, medical monitor review and approval is required. If approval to extend beyond 6 weeks ins granted, telephone or video visits should be conducted at least every 12 weeks until the in-person EOS/ET transitional visit to the other extension study is performed. The telephone or video visits will collect the following data, at minimum:

- Date and time of the telephone/video visit
- Any changes in health status
- AEs/SAE assessment
- Concomitant medication query
- Review seizure and medication diary with parent/caregiver for compliance and any abnormalities in seizure activity

4. <u>Allowance of delays to ECHO, ECG, Chest X-Ray, EEG and clinical lab assessments when in-person study visits are missed or delayed</u>

If it is not possible to obtain the assessments as described below, a documented risk/benefit discussion with the medical monitor is required to determine a course of action, which may include approval to delay further for a pre-specified duration, subject withdrawal, or other actions. The risk/benefit analysis will take into account report of drug effectiveness, 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.

<u>Doppler ECHO:</u>

If subjects are unable to travel to the study site due to COVID-19 circumstances, ECHOs may be delayed up to an additional 3 months from the protocol-designated ECHO due date (for a total of 6 months from the time of the last ECHO) for subjects that exhibited the following on their previous, most recent ECHO: absent aortic regurgitation, absent or trace mitral regurgitation, and PASP <30 mmHg.

All subjects with regurgitation ≥ trace aortic regurgitation, ≥mild mitral regurgitation, or PASP ≥30 mmHg may have ECHO delayed from the protocol-designated ECHO due date by up to 6 weeks only In those cases where an ECHO cannot be performed in the specified time period at the study-authorized facility by a certified sonographer, the Sponsor may approve administration of the ECHO at an alternative facility to minimize 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, this assessment does not need to be repeated at the Cardiac Follow-up Visit provided there were no findings meeting Level 2 criteria (see Protocol Table 12) that require additional follow-up.

<u>ECG, Chest X-ray and EEG:</u>

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. If not conducted at the study site, results should be sent to the Principal Investigator for safety overread and documentation. 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.

If the ECG (or in the case of certain country-specific regulations: Chest X-ray or EEG) was conducted within 30 days of a scheduled Cardiac Follow-up Visit, these assessments do not need to

be repeated at the Cardiac Follow-up Visit provided there were no significant findings that require additional follow-up.

Clinical Laboratory Assessments:

If clinically indicated and where applicable, delays in these assessments may be implemented based on the investigators' clinical discretion, weighing the risk/benefit of the clinical necessity of the assessment versus the risk of an in-person visit. All decisions should be documented appropriately in the source documentation. If not conducted at the study site, clinical laboratory assessments can be performed at any qualified local facility with results sent to the Principal Investigator for safety overread and documentation.

5. Alternative Dispensation for Study Drug

Shipments of investigational product may be sent by courier from site pharmacy to the subject's home via Sponsor-approved processes if the subject cannot or will not attend the dispensation visit(s). This shipment of drug should be arranged for patients who are due in the clinic for a drug dispensation visit. Other alternative dispensation, such as curbside pickup, may be implemented provided they are approved by the Sponsor and appropriate safeguards are taken to ensure compliance with existing regulatory requirements for maintaining investigational product accountability. Detailed instructions for drug handling, storage, accountability, etc. are described in the Pharmacy Manual.

SUMMARY OF PROTOCOL AMENDMENT 5.0

Clarifications and changes were made to the protocol amendment 5.0 to include study conduct information for the COVID-19 pandemic, updated background information related to existing treatments for Dravet and additional clinical and pre-clinical study data made available in the updated ZX008 IB.

List of Specific Changes

Additions are marked by underlined font and deletions are marked in ~~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 appear in the protocol.

1. Zogenix Address Change:

   Title Page and Signature Page:

Sponsor:	Zogenix International Limited A wholly owned subsidiary of Zogenix, Inc. ~~5858~~ 5959 Horton Street, [redacted] Emeryville, CA 94608 USA

2. Addition of the following text regarding transition of subjects to a separate ZX008 extension protocol or to commercial drug.

   Study Synopsis:

> After at least 1 year of treatment in Study 1503 subjects who participated in one of the core studies will transition to a separate extension study (Study 1900) once that study is approved and the study site is initiated. Continuation in a separate extension protocol will be based on benefit/risk and continued eligibility criteria being met. De novo subjects must have participated in this trial for at least 3 months with at least 1 ECHO completed and continue to meet eligibility requirements to be eligible to transition to a separate extension protocol. Alternatively, subjects will transition to commercial product once it is available. For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial. Subjects who transition to commercially available drug must have an ECHOs within 3-6 months before starting commercial drug and will have follow-up ECHOs within the required timeframe while on commercial drug.

   Table 1: Schedule of Assessments for Subjects from Core Studies ZX008-1501 and ZX008-1502, and de Novo Subjects and Table 2: Schedule of Assessments for Subjects in Core Study ZX008-1504

Table 1. Schedule of Assessments for Subjects from Core Studies ZX008-1501 and ZX008-1502, and de Novo Subjects**

Study Assessments	OLE Treatment Period					Post-Dosing	Cardiac Follow-up
Visit Number	**Visit 1[a]**	**Visit 2[c]**		**Visits 3-15 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33)**	**Visit 16[d] (EOS/ET) Month 36**	**Visit 17[g]**	**Visit 18, 19[g]**
Study Day	**-28 to 1[a]**	**15**		**30, 60, 90, 180, 270, 365, 455, 545, 635, 725. 815, 905, 995**	**1085**	**1099**	**3 and 6 months post last dose**
		Clinic	**Phone**				
Informed Consent	X						
Entry Criteria	X						
Demographics	X						
Medical/Neurological History	X[a]						
Epilepsy History	X[a,b]						
Physical Examination, complete	X[a]				X		X[e]
Physical Examination, abbreviated		X		X			X[e]
Neurological Examination, complete	X[f]				X		
Neurological Examination, abbreviated		X		X			
Vital signs	X	X		X	X		
Weight, Height, BMI	X[a]	X		X	X		
12-lead ECG	X[a]			X	X		X[e]
Doppler ECHO	X[a]			X[g,h]	X		X[e]
Urine Pregnancy Test[h]	X			X	X		
Clinical laboratory evaluation (hematology/clinical chemistry/urinalysis, etc)	X[j]	X[j]		X	X		
Urine THC Panel/Whole blood CBD	X[a]			X	X		
Plasma sample for background AEDs		X		X	X		
Tanner Staging (for subjects >7 to ≤ 18 years)	X[a]			X[k]	X		X[k]
C-SSRS	X[a]			X	X		
CGI-I (assessed by parent/caregiver)	X[a]			X	X		
CGI-I (assessed by principal investigator)	X[a]			X	X		
QOLCE	X[a]			X	X		
EQ-5D-5L (QoL of parent/caregiver)	X[a]			X	X		
HADS (Affect of parent/caregiver)	X[a]			X	X		
BRIEF	X[a]			X	X		

Table 1. Schedule of Assessments for Subjects from Core Studies ZX008-1501 and ZX008-1502, and de Novo Subjects (continued)**

Study Assessments	OLE Treatment Period					Post-Dosing	Cardiac Follow-up
Visit Number	**Visit 1[a]**	**Visit 2[c]**		**Visits 3-15 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33)**	**Visit 16[c] (EOS/ET) Month 36**	**Visit 17[g]**	**Visit 18, 19[g]**
Study Day	**-28 to 1[a]**	**15**		**30, 60, 90, 180, 270, 365, 455, 545, 635, 725. 815, 905, 995**	**1085**	**1099**	**3 and 6 months post last dose**
		Clinic	**Phone**				
PedsQL[n]	X[a]			X	X		
Study medication palatability assessment				X[l]			
Subject Diary	D	C/R/D	R	C/R/D	C/R	C/R	
Study Medication	D[b]	C/R/D	R	C/R/D	C/R/D	C/R	
Daily Diary Completion	---------- X ----------						
Concomitant Medication	X[a]	---------- X ----------					
Adverse Events	X[a]	---------- X ----------					
Adverse events of special interest	X[a]	---------- X ----------					X[m]

AED=antiepileptic drug; BMI=body mass index; BRIEF=Behavior Rating Inventory of Executive Function; C=Collect; CBD=cannabidiol; CGI-I=Clinical Global Impression-Improvement; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination; EQ-5D-5L=standardized measure of health status; HADS=Hospital Anxiety and Depression Scale; PedsQL=Pediatric Quality of Life Inventory; QoL=quality of life; QOLCE=Quality of Life in Childhood Epilepsy; R=Review

NOTE: If a subject has a birthday during the study that makes a previously unrequired assessment now required (eg, Tanner staging in a male subject who turns 8 years old during the study), this assessment(s) should be initiated at visits subsequent to the birthday.

**** de Novo subjects are subjects who did not participate in one of the core studies and may or may not be currently taking STP.**

a: For subjects enrolling from one of the core studies use data collected at Visit 12 and Visit 13 of Study ZX008-1501 or ZX008-1502.
For de novo subjects, a screening period up to 28 days is required. During this period, informed consent is required prior to any study-related procedures. All results to determine eligibility must be reviewed prior to receiving the first dose of study study medication at Visit 1.
For all subjects, clinical laboratory results and all ECHO/ECG results must be available and meet eligibility criteria prior to receiving the first dose of study medication at Visit 1.

b: De Novo subjects must meet entry criteria 3 to 7, and 10, including having had ≥4 convulsive seizures (tonic, tonic-atonic, tonic-clonic, clonic) per 4-week period for past 12 weeks prior to screening, by parent/guardian report to investigator or investigator medical notes.

c: At the discretion of the investigator, Visit 2 may be conducted as a phone visit.

d: Or early termination.

e: Follow-up ECG, ECHO, and physical examination will be performed 3 and 6 months after study completion or early termination (see Section 6.3).

f: For subjects enrolling from one of the core studies, use core study Visit 12 information unless complete neurological examination is warranted based on significant changes in subject status.

g: ECHOs will be performed at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33.

h: The Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33 ECHO may be performed any time within 3 weeks prior to the study visit. If a subject discontinues early from the study, the ECHO should be scheduled as soon as practical (see Table 7).

i: Females of child-bearing potential

j: For subjects enrolling from one of the core studies, use data collected at Visit 12 of ZX008-1501 or ZX008-1502 for Visit 1 unless clinical laboratory evaluation is warranted based on significant changes in subject status.Visit 2 clinical laboratory evaluation is optional based on subject status for all cohorts.

k: Visits 6, 15, and 27 only.

l: Visits 3 and 4 (Months 1 and 2) only.

m: Only adverse events related to cardiac safety will be collected at this visit (see Table 7).

n: Not to be completed for de novo subjects >18 years old.

o: For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial.

Table 2. Schedule of Assessments for Subjects from Core Study ZX008-1504

Study Assessments	OLE Treatment Period					Post-Dosing	Cardiac Follow-up
Visit Number	**Visit 1[a]**	**Visit 2[b]**		**Visits 3-15 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33)**	**Visit 16[c] (EOS/ET) Month 36**	**Visit 17[m]**	**Visit 18, 19[m]**
Study Day	**1[a]**	**15**		**30, 60, 90, 180, 270, 365, 455, 545, 635, 725. 815, 905, 995**	**1085**	**1099**	**3 and 6 months post last dose**
		Clinic	**Phone**				
Informed Consent	X						
Entry Criteria	X						
Demographics	X						
Medical/Neurological History	X[a]						
Epilepsy History	X[a]						
Physical Examination, complete	X[a]				X		X[d]
Physical Examination, abbreviated		X		X			X[d]
Neurological Examination, complete	X[e]				X		
Neurological Examination, abbreviated		X		X			
Vital signs	X	X		X	X		
Weight, Height, BMI	X[a]	X		X	X		
12-lead ECG	X[a]			X	X		X[d]
Doppler ECHO	X[a]			X[f,g]	X		X[d]
Urine Pregnancy Test[h]	X			X	X		
Clinical laboratory evaluation (hematology/clinical chemistry/urinalysis, etc)	X[i]	X[i]		X	X		
Urine THC Panel/Whole blood CBD	X[a]			X	X		
Plasma sample for background AEDs		X		X	X		
Tanner Staging (for subjects > 7 years old)	X[a]			X[j]	X		X[j]
C-SSRS	X[a]			X	X		
CGI-I (assessed by parent/caregiver)	X[a]			X	X		
CGI-I (assessed by principal investigator)	X[a]			X	X		
QOLCE	X[a]			X	X		
EQ-5D-5L (QoL of parent/caregiver)	X[a]			X	X		
BRIEF	X[a]			X	X		
Healthcare utilization questions	X[a]			X	X		

Table 2. Schedule of Assessments for Subjects from Core Study ZX008-1504 (continued)

Study Assessments	OLE Treatment Period					Post-Dosing	Cardiac Follow-up
Visit Number	**Visit 1[a]**	**Visit 2[b]**		**Visits 3-15 (Months 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33)**	**Visit 16[c] (EOS/ET) Month 36**	**Visit 17[m]**	**Visit 18, 19[m]**
Study Day	**1[a]**	**15**		**30, 60, 90, 180, 270, 365, 455, 545, 635, 725. 815, 905, 995**	**1085**	**1099**	**3 and 6 months post last dose**
		Clinic	**Phone**				
Karolinska Sleep Scale	X[a]			X	X		
Sleep quality/mealtime behavior questions	X[a]			X	X		
PedsQL	X[a]			X	X		
Study medication palatability assessment				X[k]			
Subject Diary	D	C/R/D	R	C/R/D	C/R	C/R	
Study Medication	D[b]	C/R/D	R	C/R/D	C/R/D	C/R	
Daily Diary Completion	---------- X ----------						
Concomitant Medications	X[a]	---------- X ----------					
Adverse Events	X[a]	---------- X ----------					
Adverse events of special interest	X[a]	---------- X ----------					X[l]

AED=antiepileptic drug; BMI=body mass index; BRIEF=Behavior Rating Inventory of Executive Function; C=Collect; CBD=cannabidiol; CGI-I=Clinical Global Impression-Improvement; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination; EQ-5D-5L=standardized measure of health status; HADS=Hospital Anxiety and Depression Scale; PedsQL=Pediatric Quality of Life Inventory; QoL=quality of life; QOLCE=Quality of Life in Childhood Epilepsy; R=Review

NOTE: If a subject has a birthday during the study that makes a previously unrequired assessment now required (eg, Tanner staging in a male subject who turns 8 years old during the study), this assessment(s) should be initiated at visits subsequent to the birthday.

a: For subjects from the core Study ZX008-1504 Cohort 1, use data collected at the last visit of the transition period; for subjects from core Study ZX008-1504 Cohort 2 use data collected at the Visit 12 and Visit 13.
For de novo subjects, a screening period up to 28 days is required. During this period, informed consent is required prior to any study-related procedures. All results to determine eligibility must be reviewed prior to receiving the first dose of study drug at Visit 1.
For subjects from ZX008-1504 Cohort 2 and de novo subjects, clinical laboratory, ECHO, and ECG results must be available and meet eligibility criteria prior to receiving the first dose of study drug at Visit 1.

b: At the discretion of the investigator, Visit 2 may be conducted as a phone visit.

c: Or early termination.

d: Follow-up ECG, ECHO, and physical examination will be performed 3 and 6 months after study completion or early termination (see Section 6.3).

e: Unless complete neurological examination is warranted based on significant changes in subject status, use data collected at the last visit of the transition period of Study ZX008-1504 Cohort 1 and for subjects from Study ZX008-1504 Cohort 2, use data collected at the Visit 12.

f: ECHOs will be performed at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33.

g: The Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and 33 ECHO may be performed any time within 3 weeks prior to the study visit. If a subject discontinues early from the study, the ECHO should be scheduled as soon as practical (see Table 7).

h: Females of child-bearing potential

i: Unless clinical laboratory evaluation is warranted based on significant changes in subject status, use data collected at the last visit of the transition period of Study ZX008-1504 Cohort 1; for subjects from Study ZX008-1504 Cohort 2, use data collected at the Visit 12. For Visit 2, clinical laboratory evaluation is optional based on subject status.

j: Visits 6, 15, and 27.

k: Visits 3 and 4 (Months 1 and 2) only.

l: Only adverse events related to cardiac safety will be collected at this visit (see Table 7).

m: For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial.

Section 3.1: Overall Study Design and Plan

Caregivers will use a diary daily to record the number/type of seizures, dosing, and use of rescue medication. A schedule of assessments is provided in **Table 1** and **Table 2**.

After at least 1 year of treatment in Study 1503 subjects who participated in one of the core studies will transition to a separate extension study (Study 1900) once that study is approved and the study site is initiated. Continuation in a separate extension protocol will be based on benefit/risk and continued eligibility criteria being met. De novo subjects must have participated in this trial for at least 3 months with at least 1 ECHO completed and continue to meet eligibility requirements to be eligible to transition to a separate extension protocol. Alternatively, subjects will transition to commercial product once it is available. For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial. Subjects who transition to commercially available drug must have an ECHO within 3-6 months before starting commercial drug and will have follow-up ECHOs within the required timeframe while on commercial drug.

3.3 STUDY DURATION

The duration of participation in the study for an individual subject is expected to be up to 158 weeks, plus follow-up safety visit 3 and 6 months after the last dose:

- OLE Treatment Period - 36 months (156 weeks)
- Post-Dosing Visit - 2 weeks after study completion or early termination
- Cardiac Follow-up (ECG and ECHO) - 3 and 6 months after study drug discontinuation for early termination and for those subjects who complete the study; not applicable to subjects who transition to commercial product.

5.4.2 Taper Period

All subjects (those who complete the OLE Treatment Period or those who discontinue from the study early and are not transitioning to another ZX008 extension study or treatment with commercial drug) will be tapered off of study medication.

6.1.5 Clinic Visit 16 (Month 36): End of Study/Early Termination

The End-of-Study participation for an individual subject occurs after he/she has received IMP for 3 years in the OLE Treatment Period or if the subject is transitioning to receive ZX008 in a separate extension protocol when available or until 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 one the following events occur:

1. The subject withdraws or is withdrawn from participation in the study.
2. The Sponsor terminates the study.
3. The subject completes all study related visits and procedures.
~~3.~~4. The subject is being transitioned to another extension study or transitioning to commercial drug.

and review with parent/caregiver

- Dispense study medication (not applicable for subjects transitioning to another extension protocol or to commercial drug)

6.2 POST-DOSE VISIT (CLINIC VISIT 17; STUDY DAY 1099)

If the subject completes the study (or discontinues from the study early), and is not transitioning to another extension protocol or switching to commercially available drug, the subject will visit the clinic on Study Day 1099 (or 14 days after the day of discontinuation)

~~and t~~The following procedures will be performed:

- Record AEs
- Record AESI
- Record concomitant medications

6.3 CARDIAC FOLLOW-UP VISIT (CLINIC VISIT 18, 19; 3 AND 6 MONTHS) AFTER LAST DOSE OF IMP

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 7. 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. Cardiac follow-up visits are not required for subjects who have entered another ZX008 extension study or have transitioned to commercial drug.

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.

If the subject is switching to commercially available drug, (subjects must have an ECHO within 3-6 months before starting commercial 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~~post dosing and cardiac follow-up visits are not required.

Section 10.4: Treatment Periods

Post-dosing Period

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

After at least 1 year of treatment in Study 1503 subjects who participated in one of the core studies will transition to a separate extension study (Study 1900) once that study is approved and the study site is initiated. Continuation in a separate extension protocol will be based on benefit/risk and continued eligibility criteria being met. De novo subjects must have participated in this trial for at least 3 months with at least 1 ECHO completed and continue to meet eligibility requirements to be eligible to transition to a separate extension protocol. Alternatively, subjects will transition to commercial product once it is available if they have had an ECHO within 3-6 months before starting commercial drug. For subjects who are entering the separate extension trial or who transition to commercially available drug, post-dosing and cardiac safety follow-up visits are not required in this trial. Subjects who transition to commercially available drug will have follow-up ECHOs within the required timeframe while on commercial drug.

3. Update to include Japan in list of participating centers

3.4 NUMBER OF STUDY CENTERS

The study expects to use up to approximately 75 research centers in North America, Europe, ~~and~~ Australia and Japan.

4. Updated background information related to existing treatments for Dravet and additional clinical and pre-clinical study data made available in the updated ZX008 IB.

1. INTRODUCTION

1.1 BACKGROUND INFORMATION ON INDICATION STUDIED

ZX008 (fenfluramine hydrochloride) is under clinical development for the adjunctive treatment of patients with Dravet syndrome (DS) 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.

Dravet syndrome, previously known as severe myoclonic epilepsy of infancy (SMEI), is a rare and severe form of epilepsy first described by Charlotte Dravet in 1978 (Dravet 1978). The International League Against Epilepsy (ILAE) considers Dravet syndrome a developmental and epileptic encephalopathy, "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).

Dravet syndrome is estimated to affect 1 out of every 15,700 live births in the US and less than 1 in 20,000 persons in the European Union (Wu 2015; EMA 2014). Dravet syndrome is responsible for 7% of the severe epilepsies starting before the age of 3 years (Ceulemans 2004).

The diagnosis of Dravet syndrome is based on clinical signs and symptoms, though the presence of a mutation in the SCN1A gene is considered a likely, though not definitive, marker for the disorder (Dravet 2011; Fujiwara 2006). Dravet syndrome is usually not diagnosed until at least 1 year of age (Cooper 2016) and is characterized by medically intractable seizures along with motor and neurodevelopmental comorbidities. Onset of the first seizure typically occurs in the first year of life (usually at 5 to 8 months of age) in otherwise healthy infants and most often consists of prolonged, unilateral or generalized, clonic seizures provoked by fever (Orphanet 2014; Ceulemans 2004; Dravet 2011). These patients will have poor response or worsening seizures to standard antiepileptic drugs, in particular, sodium channel antagonist medications (Dravet 2011).

After the first year, other types of seizures often begin to occur with high frequency and include (1) convulsive seizures consisting of generalized clonic seizures, generalized tonic-clonic (GTC) seizures or alternating unilateral clonic seizures (in the youngest patients, they often evolve into status epilepticus [SE]); (2) myoclonic seizures (appearing between the ages of 1 and 5 years); (3) atypical absences (appearing at different ages between 4 months and 6 years or later); (4) focal seizures with or without secondary generalization (appearing between the ages 4 months and 4 years); or (5) rarely, tonic seizures (TS) (Dravet 2011). Individuals with Dravet syndrome are at higher risk for SE that often results in injury and hospitalization (Ceulemans 2004). A high incidence for SUDEP (sudden expected death in epilepsy) exists in

Dravet syndrome with the major risk factor being the frequency of generalized tonic-clonic seizures (Harden 2017).

Dravet syndrome is highly treatment-resistant and affects infants, children, adolescents, and adults. In general, convulsive seizure semiology is similar in patients across ages, although seizures tend to become less frequent and less severe in patients with Dravet syndrome as they enter adulthood (Lagae 2018). Generalized convulsive seizures, mostly reported as generalized tonic-clonic seizures persist into adulthood, often with a focal onset. These seizures are less frequent than in childhood and are mostly nocturnal. Some of these major convulsive seizures may have less typical aspects, for example, bilateral or asymmetric tonic posturing, followed in some cases by a tonic vibratory state or clonic movements (Oguni, 2001; Akiyama 2009). Throughout the lives of patients with Dravet syndrome, frequent and disabling seizures are associated with significant neurobehavioral, cognitive, developmental, and motor comorbidities.

~~DS, also known as severe myoclonic epilepsy of infancy (SMEI), is a rare and severe form of epilepsy first described by Charlotte Dravet in 1978 (Dravet 1978). The condition most commonly appears during the first year of life as frequent febrile seizures. As the condition progresses, other types of seizures typically occur, including myoclonic seizures and status epilepticus (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. Dravet children 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 DS 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.~~

1.1.1 Existing Treatment for Dravet Syndrome

Currently no treatment algorithm exists for Dravet syndrome as recommended by the ILAE (International League Against Epilepsy) or any other similar medical entity. The main treatment goal in Dravet syndrome aims to reduce the frequency, duration, and severity of seizures with the ultimate goal of complete or near-complete seizure-freedom (Wirrell 2017). Attaining seizure-freedom or near seizure-freedom may be particularly important during the early developmental years. However, even with currently available AED polypharmacy,

seizure-freedom or near seizure-freedom is rarely achieved (Dravet 2000; Dravet 2005, Dravet 2011, Chiron 2011). Commonly prescribed anticonvulsant medications, the sodium channel antagonists such as phenytoin and carbamazepine, exacerbate seizures in Dravet syndrome and are thus not useful (Wirrell 2016). Treatment for Dravet syndrome involves finding the best combination of medicines to treat seizures with tolerable side effects, preventing SE, and reducing comorbidity and mortality risk. Elimination or significant reduction of prolonged convulsive seizures and SE should represent the highest priority in treatment (Wirrell 2017).

Stiripentol and cannabidiol are the only 2 treatments approved for seizures associated with Dravet syndrome.

Other therapies, topiramate (TPM), levetiracetam (LEV), and bromide may provide efficacy as adjunctive therapy for some patients (Chiron 2011). Published uncontrolled studies with LEV (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 (IV) 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.

Due to the severe and refractory nature of seizures associated with Dravet syndrome and given the risks of premature death from SUDEP, cognitive deficits, and other neurological consequences, there remains an urgent unmet medical need for the treatment of convulsive seizures associated with Dravet syndrome. The frequent and disabling seizures of different types, and the associated significant neurobehavioral, cognitive, developmental, and motor comorbidities that characterize Dravet syndrome, have a major negative impact on the patient's quality of life, as well as on their families. The neurobehavioral, cognitive, developmental, and motor comorbidities are at least partly caused by the poor control of seizures resulting in ongoing damage to the brain (Wolff 2006; Ragona 2011; Nabbout 2013; Wirrell 2016). A high incidence for SUDEP exists in Dravet syndrome with the major risk factor being the frequency of generalized tonic-clonic GTC seizures.

Dravet syndrome drains a family emotionally, physically, and financially. Parents/caregivers suffer emotional exhaustion and anxiety related to the "fear of the next seizure" and "will this be the seizure that kills my child" (Campbell 2018). Patients with the highest seizure frequency tend to have more comorbidities and a lower quality of life (Lagae 2017). A 2006 study identified the challenges faced by parents caring for children with Dravet syndrome, reporting that the combination of persistent, severe seizures, together with developmental, behavioral, and sleep issues result in a high caregiver stress load with little ability to find respite and relief (Nolan 2006). The comorbid conditions, high mortality, disorder management requirements, and difficulties with family adaptation result in constant distress (Skluzacek 2011). In addition, Dravet syndrome is associated with extensive healthcare costs due to increased medical care

use and intensive caregiver supervision as well as indirect burdens such as losses of productivity, family time, and leisure (Whittington 2018). The unremitting seizure episodes account for a high degree of healthcare resource utilization including hospitalizations, emergency room visits, and emergency transport services (Strzelczyk 2014). Aras and coworkers report 4 or more emergency room admissions in > 10% of children and up to 30 admissions per year for some (Aras 2015). The impacts of Dravet syndrome typically not considered by healthcare professionals when making treatment decisions include the child's expressive and receptive communications with family members, disruption of daily activities, and caregivers' social interactions (Villas 2017; Nabbout 2013).

A more effective treatment for Dravet syndrome that will abolish or significantly reduce seizure activity in a higher proportion of patients and provide periods of seizure freedom is urgently needed. Moreover, such outcomes could also lessen chronic brain injury and neuroinflammation due to unremitting seizures and thus potentially also improve Dravet syndromes' associated comorbidities.

~~DS is a highly treatment resistant and refractory epilepsy syndrome. Establishment of a seizure-free condition in affected children, even with anticonvulsant drug polypharmacy, is extremely rare, since all seizure types in DS appear to be drug resistant, with minimal improvement on currently available anticonvulsant drug therapies (Dravet 2000; Dravet 2005). Moreover, classic anticonvulsant medications whose mechanism is via sodium channel blockade, such as phenytoin and carbamazepine, increase these children's seizure frequency and severity.~~

~~To date, only one treatment, Diacomit® (stiripentol) is approved, and only in Canada, Europe, Japan, and Australia as adjunctive therapy in patients with SMEI (Dravet syndrome), and must be co-administered with clobazam (CLB) and valproate (VPA). STP has not been approved for use in the United States of America (USA), but is available under compassionate use protocols at certain clinical sites.~~

~~The results of an online parent-reported survey to collect information on the demographics, clinical characteristics and use of antiepileptic medications by European patients with DS was recently reported (Aras 2015). The survey took place from May to June 2014 and included two hundred seventy-four patients from 15 European countries. Most patients were 4-8 years old, and 90% had confirmed mutations in SCN1A. Their epilepsy was characterized by multiple seizure types, and 15% of the population reported more than 4 tonic-clonic seizures per month. In spite of the availability of an array of antiepileptic medications, the most common drug combination was CLB, VPA, and STP, with 42% of the patients currently taking STP.~~

~~Despite treatment with multiple antiepileptic medications, emergency room admissions for SE were common during the previous 12 months. In both the total population and the subpopulation with >4 tonic-clonic seizures per month, approximately one-third of the patients had one or more continuous, unremitting seizures requiring emergency room admission. Twenty-eight patients (10%) reported 4 or more emergency room admissions with some~~

reporting as many as 30 admissions for SE. In addition to severe epilepsy with multiple seizure types, respondents reported several co-morbidities that extended beyond seizures, including sleep disturbances, motor impairment, and abnormal socialization. Therefore, there remains a need for new medications that provide better seizure control, as well as preserve or improve the behavioral and cognitive components of DS.

For over 27 years, fenfluramine has been used as an unlicensed medicine in Belgium at 2 academic medical centers, currently using an approved protocol under a Belgium Royal Decree (government approved prospective observation trial) for the treatment of DS; the efficacy and safety of this therapeutic approach have been published in a peer reviewed journal and reported to be very favorable. Since there are no treatments specifically approved for the treatment of DS in the USA, and only 1 treatment approved in Canada and Europe, there remains an unmet need for an approved treatment for children with DS.

1.1.2 Other Antiepileptic Medications

The following antiepileptic drugs (AEDs) are approved in the USA, European Union, Canada, and Australia: valproate, topiramate, carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, benzodiazepines, phenobarbital, potassium bromide, ethosuximide, phenytoin, and vigabatrin. The treatment of DS frequently requires a combination of two or three of these compounds, but with continued suboptimal seizure control. It cannot be assumed that because a treatment has been shown to be effective in common seizure types, that it will be effective in DS. In fact, some commonly used anti-epileptic drugs with a sodium channel mechanism of action, such as carbamazepine, oxcarbazepine, phenytoin, and lamotrigine, make DS worse.

A review of the treatment modalities used for DS has been published by Chiron and Dulac (Chiron and Dulac 2011). This review indicates that valproate is commonly used as a first-line agent to prevent the recurrence of febrile seizures and oral/nasal/rectal benzodiazepine is used for any long-lasting seizures. However, the authors comment that these agents are most often insufficient. These author experts state that lamotrigine, carbamazepine, and high doses of intravenous phenobarbital should be avoided because they may worsen seizures and that topiramate, levetiracetam and bromide may provide substantial efficacy as adjunctive therapy for some patients. The authors comment that the benefit of these compounds is mild and there are no trials to validate the impression of any effect.

Given the cognitive consequences believed to be caused, at least in part, by frequent childhood seizure activity, there is a medical need for a new anticonvulsant treatment that can significantly reduce seizure activity in DS. There is the possibility that early, effective seizure control could be disease modifying, leading to an improvement in longer-term outcomes with respect to motor impairment, behavioral issues, and cognitive function.

1.2 BACKGROUND INFORMATION ON STUDY PRODUCT

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

Fenfluramine was introduced in the USA in 1973. Products containing fenfluramine and D-fenfluramine were withdrawn from the USA market in 1997 after reports of heart valve disease and pulmonary hypertension (Connolly 1997; CDC 1997; Wong 1998). While the risk/benefit relationship for fenfluramine is thus considered unfavorable for the treatment of obesity in adults, establishing seizure control in DS or any of the catastrophic childhood epilepsies might lead to a more acceptable risk/benefit profile for fenfluramine, especially if lower doses can be used successfully.

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 IB 2016~~ZX008 IB). There is also a large body of information concerning its clinical safety profile.

1.3 CLINICAL DATA

~~The first randomized, double-blind, Phase 3 study (Study 1) of ZX008 in children and young adults with DS was completed in September 2017. Study 1 investigated two doses (0.8 and 0.2 mg/kg/day) of ZX008 (fenfluramine HCl oral solution) and included 119 subjects with DS from North America, Western Europe and Australia. The primary objective of Study 1 was to evaluate ZX008 0.8 mg/kg/day (max 30 mg/day) versus placebo in controlling convulsive seizures over the 14 week treatment period. Key secondary objectives were a comparison of the ≥50% Responder Rate, and the median change in longest seizure free interval between the treatment groups. The dose of 0.2 mg/kg/day was tested versus placebo on the same endpoints as key secondary efficacy measures. Safety and tolerability were evaluated by recording adverse events (AE) and vital signs, and investigations of hematology, chemistry, ECHO, and electrocardiogram. Blood samples were collected to evaluate population PK.~~

~~Study 1 met the primary objective with high statistical significance ($p<0.001$). Subjects randomized to ZX008 0.8 mg/kg/day achieved a 63.9% reduction in mean monthly (28 days) convulsive seizure frequency (CSF) compared with placebo group reduction during combined titration and maintenance periods. Subjects randomized to ZX008 0.2 mg/kg/day achieved a~~

~~reduction in mean monthly CSF of 33.7% compared to placebo. Study 1 met all key secondary endpoints, for both the 0.8 mg/kg/day and 0.2 mg/kg/day groups.~~

~~ZX008 was generally well tolerated in Study 1. The incidence of treatment emergent AEs (TEAEs) was higher in the ZX008 treatment groups compared to the placebo group, with 38 (95.0%) subjects in the 0.8 mg/kg/day group and 37 (94.9%) subjects in the 0.2 mg/kg/day group experiencing at least one TEAEs compared to 26 (65.0%) subjects in the placebo group. The most common TEAEs (≥10%) in subjects taking ZX008 decreased appetite, diarrhea, pyrexia, echocardiogram abnormal, nasopharyngitis, lethargy, somnolence, seizure, vomiting, diastolic blood pressure increased, and weight decreased. No clinical or echocardiographic evidence of cardiac valvulopathy or pulmonary hypertension was recorded in any subject; the adverse events of echocardiogram abnormal were confined to findings of trace regurgitation on echocardiogram. No patient discontinued participation or required a change in monitoring in the study due to cardiac factors.~~

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.

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 [redacted] who was discontinued from the study; SAEs of seizure leading to hospitalization, drowsiness, reduced appetite, and weight loss in a [redacted] 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 [redacted] in the placebo group; lethargy in a [redacted] 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 for more detailed information on the safety and efficacy of ZX008 ~~in Dravet syndrome~~.

1.4 Preclinical Data

The pharmacokinetics (PK) of fenfluramine, norfenfluramine and their respective isomers has 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. ~~In humans, 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 on~~f~~ ZX008 are available in the Investigator's Brochure (ZX008 IB ~~2017~~).

1.5 Pharmacokinetics

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.

Study 1 and Study 1504 Cohort 2

Pharmacokinetic parameters of fenfluramine and norfenfluramine for patients with Dravet syndrome were determined using a population pharmacokinetic (PopPK) model developed using PK data from both healthy volunteers and patients with Dravet syndrome, and are provided in the Table 3 below.

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

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

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

Study 1504 Cohort 2 required STP as a concomitant medication. Although the dose of ZX008 in Study 1504 Cohort 2 was lower than the high dose in Study 1, fenfluramine AUC_{0-24} values were approximately 130% higher in Study 1504 Cohort 2, than the high dose in Study 1, and norfenfluramine AUC_{0-24} values were approximately 60% lower than in Study 1. However, the clinical results indicated that the efficacy and AE profile were similar between Study 1 and Study 1504, indicating that the dose adjustment studied for the concomitant use of the STP regimen met the intended clinical outcome.

1.6 Clinical Pharmacology

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

- Coadministration of ZX008 with the STP regimen (STP with CLB and/or VPA) resulted in an increased fenfluramine and decreased norfenfluramine concentrations, and therefore a dose adjustment is used in the clinical trials.

- STP is the predominant perpetrator of the interaction; while VPA and CLB do not have a significant independent impact on the PK of fenfluramine or norfenfluramine, whether administered with or without STP.
- Coadministration of ZX008 with CBD at steady state resulted in increased fenfluramine concentrations but this increase was within the range of safe dosing used in Study 1504 Cohort 2; thus, no dose adjustment is recommended when fenfluramine is coadministered with CBD.
- In the population PK analysis, intrinsic patient factors (age, gender, race/ethnicity, and BMI) demonstrated no substantial impact on the clearance or exposure to fenfluramine or norfenfluramine when dosed on a mg/kg basis to a maximum of 30 mg/day.
- ZX008 had no effect on QTc intervals at either the therapeutic or supratherapeutic dose, and no relationship was observed between fenfluramine or norfenfluramine exposure and QTcF.
- ZX008 exhibited approximately dose proportional PK over a 4-fold range of doses (15 to 120 mg/day).
- CYP450 metabolizer genotype for CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 had no impact on the PK of fenfluramine or norfenfluramine.

5. Updates to the data available for Risk-Benefit Section 1.8

~~1.8~~1.10 RISK-BENEFIT ASSESSMENT

Fenfluramine has been used successfully for ~~up to 27~~up to 30 years in Belgium in refractory pediatric epilepsy patients, including those with DS (Boel 1996, Ceulemans 2012, Ceulemans 2016, Schoonjans 2016, Schoonjans 2017). The efficacy and safety of this therapeutic approach has been reported to be overwhelmingly favorable. Of the 15 DS treated patients, 10 (67%) were reported as seizure-free, with the average time of seizure-freedom being 6 years (range 1-19 years). Twelve patients (87%) had a greater than 90% reduction in seizure frequency and 14 patients (93%) with greater than 70% reduction in seizure frequency. No patients experienced emergence of clinical valvulopathy or pulmonary hypertension. The doses tested thus far in DS range from 0.12 to 0.9 mg/kg/day in subjects over 1 year of age to adults. Fenfluramine has also been administered to over 500 children with neurobehavioral conditions, including autism and ADHD with good safety and tolerability. Doses tested in these pediatric studies ranged from 0.65 mg/kg/day to 3.6 mg/kg/day, but a commonly used dose was 1.5 mg/kg/day. Occasionally, fixed doses of 30 to 80 mg were used.

In addition, ZX008 demonstrated a statistically significant and clinically meaningful reduction in monthly convulsive seizure frequency in Study 1 and Study 1504 Cohort 2 and was generally well tolerated. There was no clinical or echocardiographic evidence of cardiac valvulopathy or pulmonary hypertension ~~in Study 1~~ and no patient discontinued participation or required a change in monitoring in the study due to cardiac factors. The PK exposure associated with the doses of ZX008 in the DS studies of 0.2 mg/kg/day to 0.8 mg/kg/day administered orally [in equally divided doses twice per day (BID)] is expected to be lower than that obtained at the doses used in the past for the treatment of obesity in adults and of neurobehavioral conditions in children and adolescents (ZX008 IB ~~2017~~). The doses used in this study are based on the data from the DS patients being successfully treated in Belgium discussed above and supported by results from Study 1 and Study 1504 Cohort 2.

Interim results from this open-label study show that the effects observed during the double-blind studies were durable and long-lasting; the reduction in convulsive seizures for subjects in Study 1503, was maintained throughout study participation of up to 3 years at the time of the interim analysis, with no evidence for developing tolerance. The pharmacologic and toxicological profile for the active pharmaceutical ingredient, fenfluramine, following oral administration is well established (~~ZX008 IB 2017~~ZX008 IB).

6. Reference to ZX008 IB 2016 updated to ZX008 IB.

7. Provides study conduct information during the COVID-19 Pandemic

6. VISIT SCHEDULE

Study procedures will be conducted according to the Schedule of Assessments in **Table 1** and **Table 2**. Time windows for all assessments are detailed in Table 6. For details on alternative procedures and allowances regarding study conduct during COVD-19 refer to Appendix 11.

6.5 STUDY CONDUCT DURING COVD-19

In March 2020, the World Health Organization declared a global pandemic related to an illness caused by a novel coronavirus known as COVID-19. Alternative procedures and allowances are permitted due to restrictions related to COVID-19, including delays to in-person visits and specific assessments, performing remote phone or video visits if in-person visits cannot be conducted, and arranging shipments of investigational product directly to subjects. These allowances are detailed in Appendix 11. Though every attempt should be made to conduct study visits as described in this protocol, any implementation of alternative processes should be properly documented, including what was done differently, which assessments or visits were missed or performed via phone or video.

14.11 APPENDIX 11 - 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 15, 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 ~~in-person~~specific visits; assessment forms located within a particular visit page will also be entered normally, however, queries will be fired to capture specific information explaining the basis for missing or alternatively collected (ie. remote) data. Detailed instruction for EDC entry may be found in the CRF Completion Guidelines (CCGs).

- Date and time of the telephone/video visit
- Any changes in health status
- AEs/SAE assessment
- Concomitant medication query
- Review seizure and medication diary with parent/caregiver for compliance and any abnormalities in seizure activity
- Scales and Questionnaires, when applicable and if feasible
  - C-SSRS

- CGI-I (by Investigator)
- Tanner Staging

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

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

EOS/ET for subjects tapering off ZX008:

For the EOS/ET visit (Visit 16) and Post-Dosing Follow-up visits~~(Visits 17-19)~~, 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 more than 6 months have passed, subjects will be considered lost to follow up.~~ 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.

EOS/ET for subjects transitioning to Commercial drug:

For the EOS/ET visit (Visit 16) and Post-Dosing Follow-up visit (Visit 17), 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 an ECHO within 3-6 months before starting commercial drug and will have follow-up ECHOs within the required timeframe while on commercial drug.

EOS/ET for subjects transitioning to another extension study:

For subjects transitioning into another ZX008 extension study that are unable to attend the EOS/ET visit due to restrictions to traveling to the study site, delays in the start-up of the extension study, or other COVID-related delays, the EOS/ET visit may be delayed until an in-person visit is conducted. Therefore, subjects may remain on study for longer than the planned duration of participation. If the delay is over 6 weeks, medical monitor review and approval is required. If approval to extend beyond 6 weeks ~~is~~ granted, ~~Additionally,~~ telephone or video visits should be conducted at least every 12 weeks until the in-person EOS/ET transitional visit to the other extension study is performed. The telephone or video visits will collect the following data, at minimum:

- Date and time of the telephone/video visit
- Any changes in health status
- AEs/SAE assessment
- Concomitant medication query
- Review seizure and medication diary with parent/caregiver for compliance and any abnormalities in seizure activity

4. **Allowance of delays to ECHO, ECG, Chest X-Ray, EEG and clinical lab assessments when in-person study visits are missed or delayed**

If it is not possible to obtain ~~any of the above~~ assessments as described below, a documented risk/benefit discussion with the medical monitor is required ~~and must be documented~~ 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 report of drug effectiveness, 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:

~~Must be conducted at the study authorized facility by certified sonographers. , unless an alternative is approved by the Sponsor.~~

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 ~~(for a total of 6 months from the time of the last ECHO)~~ from the protocol-designated ECHO due date (for a total of 6 months from the time of the last ECHO) for subjects that exhibited the following on their previous, most recent ECHO: absent aortic regurgitation, absent or trace mitral regurgitation, and PASP <30 mmHg.

All subjects with regurgitation ≥ trace aortic regurgitation, ≥mild mitral regurgitation, or PASP ≥30 mmHg may have ECHO delayed from the protocol-designated ECHO due date by up to 6 weeks only.

In those cases where an ECHO cannot be performed in the specified time period at the study-authorized facility by a certified sonographer, the Sponsor may approve administration of the ECHO at an alternative facility to minimize subject's need for travel~~If needed, the sponsor will provide a list of pediatric echo centers ('brick and mortar' locations) certified by Intersocietal Accreditation Commission (IAC).~~ 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, this assessment does not need to be repeated at the Cardiac Follow-up Visit provided there were no findings meeting Level 2 criteria (see Protocol Table 12) that require additional follow-up. 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. If not conducted at the study site, results should 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:

If clinically indicated and where applicable, delays in these assessments may be implemented based on the investigators' clinical discretion, weighing the risk/benefit of the clinical necessity of the assessment versus the risk of an in-person visit. All decisions should be documented appropriately in the source documentation. If not conducted at the study site, clinical laboratory assessments can be performed at any qualified local facility with results sent to the Principal Investigator for safety overread and documentation.

~~Laboratory assessments may be delayed up to 6 weeks. Local labs may be conducted if clinically indicated or if delays are expected to be >8 weeks; local lab results are to be sent to the Principal Investigator for safety overread.~~

5. Alternative Dispensation for Study Drug ~~Alternative Dispensation~~

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.

8. Table 11 updated to Table 12. Table was amended to reflect the latest safety database, contained in the NDA and MAA and updated in the 120-day Safety update, the lack of appearance of valvular heart disease or PAH in any subject supports the removal of IDSMC oversight of mild mitral regurgitation in children. It further supports utilization of the Level 2 review for moderate mitral, pulmonic and tricuspid regurgitation in the absence of any indicators of PAH.

Table 11. Clinical Measures Enacted Upon Increasing Severity of ECHO Findings

Severity	Valve			
	Aortic	Mitral	Pulmonary	Tricuspid
~~Trace (≤18 years)~~	~~Level 2~~	~~Level 2~~	~~Level 1~~	~~Level 1~~
Trace ~~(>18 years)~~	Level 1	Level 1	Level 1	Level 1
Mild (≤18 years)	Level 2	Level 12	Level 1	Level 1
Mild (>18 years)	Level 2	Level 1	Level 1	Level 1
Moderate	Level 3	Level 23	Level 23	Level 23
Severe	Level 3	Level 3	Level 3	Level 3