STATISTICAL ANALYSIS PLAN

Study Title	An Open-Label Extension Trial to Assess the Long-Term Safety of ZX008 (Fenfluramine Hydrochloride) Oral Solution as an Adjunctive Therapy for Seizures in Patients with Rare Seizure Disorders Such as Epileptic Encephalopathies Including Dravet Syndrome and Lennox-Gastaut Syndrome
Study Number:	ZX008-1900/EP0215
Study Product:	Fenfluramine Hydrochloride Oral Solution; ZX008
IND Number:	125797, 132604
EudraCT:	2019-001331-31
Sponsor:	Zogenix International Limited an indirectly wholly owned subsidiary of Zogenix Inc. which is a directly wholly owned subsidiary of UCB Biosciences, 4000 Paramount Pkwy, Suite 200, Morrisville, NC 27560, USA
Date/Version of Study Protocol:	22 September 2022 (Amendment 4.0) 22 September 2022 (Amendment 4.1-FR) 22 September 2022 (Amendment 4.1-Sweden) 22 September 2022 (Amendment 4.1-UK) 20 November 2020 (Amendment 3.1.1 DK)

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REVISION HISTORY

Version #	Date (DD-MMM-YYYY)	Document Owner	Revision Summary
1.0	11-Jan-2021	[redacted]	Initial Release Version
2.0	11-May-2021	[redacted]	1. United Kingdom and Denmark protocols added 2. Clarified timepoint reporting for the study is in months for tables, listings, and figures; added visit, month, day table. 3. Clarified that the mITT population requires at least one efficacy result after Visit 1 in the OLE. 4. Revised definitions of most extreme abnormal vital sign and lab values. 5. Added detail to the calculation of mean daily to include caps on daily dosage. 6. Added a summary of the exposure adjusted TEAE incidence rate. 7. Added additional CGI tables and listings. 8. Added frequency tables to TFL TOC to include most extreme abnormal values for vital signs and lab values. 9. Updated TFL Table of Contents. 10. Mean daily dose calculation updated. 11. Terminology updates throughout document.

Version #	Date (DD-MMM-YYYY)	Document Owner	Revision Summary
3.0	29-Nov-2021	[redacted]	12. Updated TFL table of contents to match Interim Analysis and 120-day safety update outputs. 13. Amendment purpose statement added. 14. Efficacy outputs updated to reflect additional CGI-I and CGI-S outputs included in the Interim Analysis. 15. Updated mean daily dose to exclude volume in the calculation. 16. Updated demographics and baseline characteristics table requirements to include CGI-S modifications and regional modifications. 17. Compliance definition updated. 18. Mean daily dose definition and requirements updated. 19. C-SSRS categories updated to include reporting of Self-Injurious Behavior Without Suicidal Intent.

Version #	Date (DD-MMM-YYYY)	Document Owner	Revision Summary
4.0	27-Oct-2023	[redacted]	20. Revised to reflect changes made in the Study Protocol Amendment 4.0 and country-specific Protocol Amendments 4.1-FR and 4.1-UK. 21. Updated/clarification of responsibilities. 22. Enrolled population added. 23. General methods updated to align with UCB standards. 24. Last on-treatment summary visit added for final analysis. 25. Visit windowing added for Month 36. 26. Clarification that except for ECHO the Visit 1 value will be the Baseline value (if no data recorded at Visit 1 then Baseline will be missing). 27. Calculation of mean daily dose clarified. 28. Definition of study completer clarified. 29. Clarification of treatment exposure and compliance calculations. 30. Handling of laboratory results recorded as <X or >Y clarified.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	adverse event
AED	antiepileptic drug
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CDD	CDKL5 deficiency disorder
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CI	confidence interval
CRF	case report form
CRO	contract research organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV SAP	cardiovascular statistical analysis plan
ECG	electrocardiogram
ECHO	echocardiogram
EEG	electroencephalogram
EOS	End of Study (Visit)
ET	Early Termination (Visit)
FR	France
ICF	informed consent form
IDSMC	Independent Data and Safety Monitoring Committee

Abbreviation / Acronym	Definition / Expansion
kg	kilogram
LGS	Lennox-Gastaut syndrome
LH	luteinizing hormone
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg/day	milligram per kilogram per day
min	minutes
mITT	modified Intent-to-Treat
mL	milliliter
NL	Netherlands
OLE	open-label extension
PT	preferred term
SAE	serious adverse event
SAF	Safety Population
SD	standard deviation
SE	status epilepticus
SoA	schedule of assessments
SOC	system organ class
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy
TEAE	treatment emergent adverse event
TFLs	tables, figures and listings

Abbreviation / Acronym	Definition / Expansion
UK	United Kingdom
USA	United States of America
VNS	vagal nerve stimulator/stimulation
ZX008	fenfluramine hydrochloride oral solution

1 INTRODUCTION

Fenfluramine hydrochloride oral solution (ZX008) is under clinical development for the adjunctive treatment of seizures associated with Dravet syndrome, Lennox-Gastaut syndrome (LGS), and CDKL5 deficiency disorder (CDD), three rare seizure disorders classified as epileptic encephalopathies by the International League Against Epilepsy. Fenfluramine (Fintepla®) is authorized for sale in the United States, Europe, and the United Kingdom for the treatment of seizures associated with Dravet syndrome and LGS, and in Japan for Dravet syndrome in patients 2 years of age and older.

An epileptic encephalopathy is "a condition in which the epileptic activity itself may directly contribute to 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, et al., 2017).

The present ZX008-1900/EP0215 study enrolled only Dravet syndrome and LGS participants. Future development plans for ZX008 may include other rare epilepsy disorders and other epileptic encephalopathies.

1.1 About Dravet Syndrome

Dravet Syndrome is a rare and severe form of epilepsy first described by Charlotte Dravet in 1978 (Dravet, 1978). The condition most commonly appears during the first year of life as frequent febrile seizures. As the condition progresses, other types of seizures typically occur, including myoclonic seizures and status epilepticus (SE). Following the appearance of these seizures, affected children develop several co-morbid conditions including psychomotor regression, ataxia, sleep disturbance, and cognitive impairment (Gataullina & Dulac, 2017). Intellectual impairment begins to become apparent around age 2 years due to lack of intellectual/behavioral progression. Children with Dravet syndrome often have a lack of coordination, poor development of language, hyperactivity, and difficulty relating to others (Dravet, 2011) (Zuberi, et al., 2022). The degree of cognitive impairment appears to correlate, at least in part, with the frequency of seizures, and might be a result of repeated cerebral hypoxia. Children with Dravet syndrome also encounter a higher incidence of sudden unexpected death in epilepsy (SUDEP) than other populations with epilepsy (Sullivan, et al., 2022). Indirect evidence has linked SUDEP to several possible etiologies, including seizure-induced apnea, pulmonary edema, dysregulation of cerebral circulation, and cardiac arrhythmias (Gataullina & Dulac, 2017), although the actual etiology remains unknown and other mechanisms have not been ruled out. Most patients who survive to adulthood are wholly dependent on around-the-clock caregivers and eventually live in institutional care homes.

1.2 About Lennox-Gastaut Syndrome (LGS)

Lennox-Gastaut Syndrome is another rare and severe epileptic encephalopathy. Onset of LGS usually occurs most commonly before the age of 11 years, with a peak between 3 and 5 years of age (Arzimanoglou, et al., 2009) (Hancock & Cross, 2013). Patients with LGS account for 5% to 10% of children with seizures. The diagnosis of LGS includes clinical signs combined with typical electroencephalograph (EEG) features. The clinical presentation of LGS is heterogeneous, however LGS is always characterized by a triad of symptoms: multiple seizure types, slow spike-and-wave EEG, and abnormal cognitive development. Tonic seizures (TS), atypical absence seizures, and "drop attacks" are notable in this disorder and often result in

serious injury. Patients with LGS also can experience milder seizures that do not result in falls, as well as many other seizure types, such as generalized tonic-clonic seizures (GTC), myoclonic seizures (MS), focal seizures, and non-convulsive SE (Camfield, 2011). Nearly all LGS patients have treatment-resistant, lifelong epilepsy. Prognosis for LGS is very poor: 5% of children die, 80%–90% continue having seizures into adulthood, and nearly all have cognitive and behavioral problems (Panayiotopoulos, 2005). Children and adults with LGS have an enormous impact on their families, and efforts to improve the quality of life for these patients are complex.

2 PURPOSE & RESPONSIBILITIES

2.1 Purpose

This version (4.0) of the statistical analysis plan (SAP) has been revised to reflect changes made in the Study Protocol Amendment 4.0 and country-specific Protocol Amendments 4.1-FR and 4.1-UK. The interim analysis (with a data cutoff of 19 October 2020) and the Day 120 safety update (with a data cutoff date of 02 August 2021) analysis were performed prior to the development of version 4.0 of the SAP. The changes in this version will be used in the development of the final tables, figures, and listings (TFLs) and clinical study report (CSR).

The SAP details the statistical methodology to be used in analyzing study data and ensures the summary TFLs are appropriate to make conclusions about the study objectives.

The SAP describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol.

The analyses described in this SAP are based upon the following study documents:

- Study 1900/EP0215 Protocol, 22 September 2022 (Amendment 4.0) and country-specific Study 1900/EP0215 Protocol, 22 September 2022 (Amendment 4.1-FR), 22 September 2022 (Amendment 4.1-UK) and 20 November 2020 (Amendment 3.1.1 DK)

The country-specific Study 1900/EP0215 Protocol for Sweden, 22 September 2022 (Amendment 4.1-Sweden) does not require any analyses or details beyond what is required by Study 1900/EP0215 Protocol, 22 September 2022 (Amendment 4.0).

The SAP will be finalized prior to database lock. If circumstances should arise during the study rendering these analyses inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. SAP amendments will be recorded by a convention that includes ascending version numbers and date.

2.2 Responsibilities

Veramed Ltd will perform the statistical analyses and is responsible for the production and quality control of all datasets, specifications, and TFLs, except for information related to electrocardiograms (ECGs) and echocardiograms (ECHOs), which will be included in a separate cardiovascular SAP (CV SAP). Additionally, the SDTMs related to ECGs and ECHOs will be produced by Veramed Ltd.

A separate CV SAP that includes ECG/ECHO will be produced by Clario, a division of Biomedical Systems/ERT, and will provide details regarding ECG and ECHO data analysis. Clario will also perform the statistical analyses and is responsible for the production and quality control of all ADaM datasets, specifications, and TFLs related to ECGs and ECHOs.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

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

3.2 Secondary Objectives

To assess the effect of ZX008 on the following effectiveness measures:

- Investigator assessment of overall seizure burden assessment (<25%, ≥25%, ≥50%, ≥75%, or 100% [i.e., seizure-free] improvement)
- Clinical Global Impression – Improvement (CGI-I) rating, globally and for specific domains, as assessed by the investigator
- CGI-I rating, globally and for specific domains, as assessed by the parent/caregiver

3.3 Study Endpoints

3.3.1 Safety

The safety endpoints of the study are:

- Adverse Events (AEs)
- Laboratory safety (hematology, chemistry)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- Physical examination (if clinically indicated)
- Neurological examination (if clinically indicated)
- ECGs (if clinically indicated)
- Doppler ECHOs
- Body weight/height
- Chest x-ray (subjects in France and Netherlands [NL] only)
- EEG (in Italy only)

Laboratory safety parameters (hematology, biochemistry) and physical/neurological examinations will only be assessed as clinically indicated. In all countries except France, ECGs will only be assessed as clinically indicated. In France, only the ECGs at clinic visits 1 and 13 and chest x-rays at clinic visits 3, 5, 7, 9, and 11 will be assessed as clinically indicated; these assessments are required at the other clinic visits. Further, chest x-rays will be collected only in France and NL, and in the latter, only when clinically indicated. EEGs will be collected only in Italy, and only when clinically indicated.

3.3.2 Efficacy

The effectiveness endpoints of the study are:

- Percent improvement in seizure burden as assessed by the investigator (or designee)
- CGI-I, globally and for specific domains, as assessed by investigator (or designee)

- CGI-I, globally and for specific domains, as assessed by parent/caregiver

Assessments by the investigator (or designee) should be performed by the same rater for each subject whenever possible. If the rater changes permanently, a new baseline Clinical Global Impression – Severity (CGI-S) (refer to Appendix 3 of the Clinical Study 1900/EP0215 Protocol Amendment 4.0) should be established (see Section 7.1.2 of the Clinical Study 1900/EP0215 Protocol Amendment 4.0). The same parent/caregiver should perform each assessment. If the same parent/caregiver is not available, the assessment should be skipped.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

Study EP0215 (ZX008-1900, referred to hereafter as Study 1900) is an international, multicenter, open-label, long-term safety study of ZX008 in subjects with epileptic encephalopathy, including Dravet syndrome or LGS. Subjects eligible for participation are those with Dravet syndrome who are currently enrolled in Study EP0212 (ZX008-1503, referred to hereafter as Study 1503), or those with LGS who have successfully completed Study EP0214 (ZX008-1601, referred to hereafter as Study 1601) Part 2, and are candidates for continued treatment with ZX008 for an extended period of time, or those with Dravet syndrome, LGS, or another epileptic encephalopathy who have completed participation in another Zogenix-sponsored study and are candidates for continued treatment with ZX008 for an extended period of time and have been invited to participate in this study.

Subjects having transitioned from Study 1503 or Study 1601 or who have participated in another Zogenix-sponsored study will be eligible to participate in this trial for up to 24 months (Danish subjects only), until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subject's country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first.

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

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

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

Safety assessments and ECHOs, detailed in the Schedule of Assessments (SoA) (refer to Section 16.1 of this SAP), will be conducted every 6 months unless noted otherwise in the SoA, or more frequent follow-up is clinically indicated or required by the Sponsor or Independent Data and Safety Monitoring Committee (IDSMC). A follow-up visit and a cardiac safety assessment will be performed after study drug discontinuation for subjects who do not transition to commercially available ZX008. Subjects who transition to commercially available ZX008 will not return for a follow-up after End of Study/Early Termination Visit (EOS/ET) or a cardiac follow-up after last dose but must have had an ECHO within 3 to 6 months before the transition date and will have follow-up ECHOs within the required timeframe while on commercial drug supply.

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

4.2 Sample Size Determination

The sample size for this study is not statistically determined.

The sample size will be determined by the number of subjects who participate in Study 1503 or Study 1601 Part 2 or another Zogenix-sponsored trial and who volunteer for the extension study and meet the necessary criteria for enrollment. Up to approximately 650 subjects may be enrolled.

4.3 Duration

Subjects will be eligible to participate in this trial for up to 24-months (Denmark only), until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first.

4.4 Number of Study Centers

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

4.5 Visit Schedule

Study procedures will be conducted according to the SoA (refer to Section 16.1 of this SAP). Time windows for all assessments for study sites in all countries but Denmark, France and the UK are detailed in the table below:

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Study Day 1)	Not applicable: same as the last visit in Study 1503 or Study 1601 Part 2, or other ZX008 study as applicable
Visits 2, 3, 4, 5, 6 (Months 6, 12, 18, 24, 30; Days 180, 360, 540, 720, 900)	± 7 days
Visit 7 (EOS/ET; Month 36; Day 1080) [a]	± 7 days
Visit 8 (EOS/ET + 14 days)	
Visit 9 (Cardiac Follow-up; Last Dose + 6 months) [b]	± 7 days

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

[b] May be additional follow-up depending on country requirements. See Table 5 in the Clinical Study Protocol, Amendment 4.0, for details.

Time windows specific to study site in Denmark are detailed in the table below:

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

[a] Subjects will receive ZX008 treatment in this study for up to 24 months.

[b] See Table 5, in the Clinical Study Protocol, Amendment 3.1.1-DK, for details.

Time windows specific to study site in France are detailed in the table below:

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Study Day 1)	Not applicable: same as the last visit in Study 1503 or Study 1601 Part 2, or other ZX008 study as applicable
Visits 2, 4, 6, 8, 10, 12 (Months 3, 9, 15, 21, 27, 33; Days 90, 270, 450, 630, 810, 990)	± 7 days
Visits 3, 5, 7, 9, 11 (Months 6, 12, 18, 24, 30; Days 180, 360, 540, 720, 900)	± 7 days
Visit 13 (EOS/ET; Month 36; Day 1080) [a]	± 7 days
Visit 14 (EOS/ET + 14 days)	
Visit 15, 16, 17 (EOS/ET + 3, 6, and 24 months) [b]	± 14 days

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

[b] See Table 5, in the Clinical Study Protocol, Amendment 4.1-FR, for details.

Time windows specific to study site in the UK are detailed in the table below:

Visit / Procedure	Time window (relative to scheduled visit / procedure)
Visit 1 (Clinic; Study Day 1)	Not applicable: same as the last visit in Study 1503 or Study 1601 Part 2, or other ZX008 study as applicable
Telephone Visits 2, 4, 6, 8, 10, 12 (Months 3, 9, 15, 21, 27, 33; Days 90, 270, 450, 630, 810, 990)	± 7 days
On-Site Visits 3, 5, 7, 9, 11 (Months 6, 12, 18, 24, 30; Days 180, 360, 540, 720, 900)	± 7 days
Visit 13 (EOS/ET; Month 36; Day 1080) [a]	± 7 days
Visit 14 (EOS/ET + 14 days)	
Visit 15, 16 (EOS/ET + 6 and 12 months) [b]	± 14 days

[a] Subjects will receive ZX008 treatment in this study until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subject's country of residence, or until the

Visit / Procedure	Time window (relative to scheduled visit / procedure)

investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first. In that regard, participation could be extended beyond 36 months if none of the conditions above mentioned are met.

[b] See Table 5, in the Clinical Study Protocol, Amendment 4.1-UK, for details.

4.6 Treatment Administration

4.6.1 Open-label Extension Treatment Period

Study drug will be administered as equal doses twice daily in the morning and in the evening, approximately 12 hours apart, with or without food. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of study drug may be taken later, up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given.

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

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

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

4.6.2 Taper Period

All subjects (those who complete the OLE Treatment Period and those who discontinue from the study early) and do not transition to commercial product where approved, will be tapered off study drug.

The tapering scheme is a 2-step process described below:

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

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 0.5 mg/kg/day (for subjects taking concomitant STP)	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.6 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day
ZX008 0.8 mg/kg/day	ZX008 0.4 mg/kg/day	ZX008 0.2 mg/kg/day

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

Full details on study drug administration are included in the Clinical Study 1900/EP0215 Protocol, Amendment 4.0, 4.1-FR, 4.1-Sweden, 4.1-UK, 3.1.1-DK.

5 ANALYSIS POPULATIONS

5.1 Enrolled Population

The Enrolled Population is defined as all subjects who signed the informed consent form (ICF).

5.2 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 OLE.

If it is not possible to determine whether a subject was dosed based on compliance data, then where there is any study participation after Day 1 it is assumed that the subject received at least one dose. If there is no further study participation after Day 1 then it is assumed the subject was not dosed.

5.3 Modified Intent-to-Treat (mITT) Population

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

6 PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Deviations are major or minor.

6.1 Major

Major protocol deviations are protocol deviations that impact subject safety or have the potential to erode data integrity and/or clinical outcomes. Major protocol deviations will be summarized and presented in a table and listing, respectively, for the SAF population.

Major protocol deviations will be grouped into the following categories:

- Inclusion/Exclusion Criteria
- ICF
- Safety Reporting
- Visit Out of Window
- Missed Study Visit
- Procedure/Exam/Questionnaire not per protocol
- Procedure/Exam/Questionnaire out of window
- Concomitant Medication
- Lab Sample
- Dosing
- Other, Specify

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

Changes in study conduct due to COVID-19, any missed study visits, out of window study visits, or alternative study visits (e.g., telemedicine), missing protocol-specified procedures, and changes to ZX008 dispensation due to COVID-19 will be summarized and presented in a table for the SAF population. Deviations due to COVID-19 will be flagged in the listings of all protocol deviations, listed by subject for the SAF population.

Additional analysis may be performed to assess the impact of COVID-19 related deviations as appropriate.

7 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

7.1 Quality Assurance

Programs are used to create listings, summary tables, and figures. Veramed Ltd will follow UCB standard operating procedures which provide details associated with development, validation, and quality control of SAS programs that are used in this study.

7.2 Software

All statistical analysis and outputs will be produced using SAS® version 9.4 or later.

7.3 General Methods

Descriptive statistics, including the numbers and percentages for dichotomous or categorical variables, and the numbers, means, standard deviations (SDs), medians, minimums, and maximums for continuous variables will be provided.

When reporting percentage values, the following rules apply:

- For values where all subjects fulfill a certain criterion, the percentage value will be displayed as 100.

- For values where the absolute frequency is 0, there will be no percentage presented at all.
- All other percentage displays will use one decimal place.

The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, and 1 more decimal place than in the raw data will be presented when reporting the mean, median, and SD.

Confidence intervals (CIs) should be regarded as descriptive and not for formal inferential purposes.

Visits scheduled for France and UK only (e.g., Month 3) will not be included in summary tables and figures. All visits will be included in listings.

Safety summaries and analyses will be presented overall, and effectiveness summaries and analyses will be presented overall and by seizure disorder (Dravet syndrome or LGS) unless otherwise stated. Summaries will be presented by mean daily dose group unless otherwise stated. The following mean daily dose groups will be used for summaries:

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

If a table or listing is blank due to zero observations, then an output will be produced displaying the text "No subjects meet the criteria".

Two-sided 95% CIs will be calculated for percentages using the Clopper Pearson method by assuming 'yes' for all subjects in the selected category and 'no' for all subjects with data at the visit in a different category.

7.4 Visits & Months

Visits will be represented using months for reporting purposes. The following table details the study time intervals in terms of visit, day, and corresponding month. Study outputs will be presented using months. Labels in the SAP may be different than what exists in the trial domains. Data beyond Month 36 will not be included in 'by visit' summaries (except Last On-Treatment Visit and EOS/ET Visit).

Label on output	All countries except France, Denmark, UK	France	Denmark	UK	Planned Day
Baseline	Visit 1	Visit 1	Visit 1	Visit 1	1
Month 3		Visit 2		Visit 2	90
Month 6	Visit 2	Visit 3	Visit 2	Visit 3	180
Month 9		Visit 4		Visit 4	270
Month 12	Visit 3	Visit 5	Visit 3	Visit 5	360

Label on output	All countries except France, Denmark, UK	France	Denmark	UK	Planned Day
Month 15		Visit 6		Visit 6	450
Month 18	Visit 4	Visit 7	Visit 4	Visit 7	540
Month 21		Visit 8		Visit 8	630
Month 24	Visit 5	Visit 9	Visit 5	Visit 9	720
Month 27		Visit 10		Visit 10	810
Month 30	Visit 6	Visit 11		Visit 11	900
Month 33		Visit 12		Visit 12	990
Month 36	Visit 7	Visit 13		Visit 13	1080
Last Visit (interim analysis only)	Last recorded assessment per parameter at the data cut-off date for all subjects that have or are participating in the trial				
Last On-Treatment Visit (final analysis only)	Last recorded assessment per parameter on or before the treatment termination date for all subjects that have or are participating in the trial				
EOS/ET Visit	EOS or ET only for subjects that have exited the trial				
EOS/ET + 14 days	Visit 8	Visit 14	Visit 6	Visit 14	
Cardiac FU 3-month		Visit 15			
Cardiac FU 6-month	Visit 9	Visit 16	Visit 7	Visit 15	
Cardiac FU 12-month				Visit 16	
Cardiac FU 24-month	Visit 10 (Germany and NL only)	Visit 17			

Windowing will be performed for the Month 36 visit only. All visits recorded as Month 36 (EOS/ET) or Unscheduled with dates within a 30-day window of the Month 36 target day (Day 1050 - Day 1110) will be inspected. The visit with non-missing data that is closest to the planned day (Day 1080) will be labelled Month 36. If there are multiple visits equidistant then the earliest visit with non-missing data will be selected.

7.5 Missing Data

The term missing date refers to a completely missing date or to an incomplete date/partial date where parts are not available, e.g., missing month/day/year.

If there is missing data for a categorical summary, there will be a row showing the number and percentage of subjects with missing values.

7.5.1 Missing Start and End Dates

Missing adverse event (AE) start dates will be imputed conservatively, i.e., missing values will be imputed in such a way that the duration of the AE is considered with the longest possible duration and such that, whenever the AE may potentially start after first date of study drug, the AE will be handled as a treatment-emergent adverse event (TEAE).

Whenever a medication may potentially start prior to ZX008 treatment and end after Visit 1, that medication will be assumed to be prior and concomitant (i.e., assume it started prior to ZX008 treatment in Study 1900 and continued into the treatment period).

The partial/missing start date of an AE or prior/concomitant medication will be imputed for the purpose of calculating TEAE status and prior/concomitant medication status. Definitions are provided in the following table. Imputed dates will not be presented in the listings.

Partial/ Missing Start date	Adverse Event	Missing day – If day is missing but month and year are present, then impute the 1st of the month, unless month is same as month of Visit 1, in which case impute Visit 1 date. Missing day and month – If day and month are both missing but year is present, then impute 1st January, unless year is the same as year of Visit 1, in which case impute Visit 1 date. Completely missing – If start date is completely missing, then impute Visit 1 date. Note: if these rules lead to imputing a start date after a known end date, impute 1st January of the year of the end date.
	Prior and Concomitant Medication	Missing day – If day is missing but month and year are present, then impute the 1st of the month. Missing day and month – If day and month are both missing but year is present, then impute 1st January. Completely missing – If start date is completely missing, then impute whichever is earlier from: 1st January of the same year as the end date (if the year of end date is known) or Visit 1 date minus 1 day.

		Note: if these rules lead to imputing a start date after a known end date, impute 1st January of the year of the end date.

7.6 Key Definitions

7.6.1 Baseline

The baseline value will be the value collected at Visit 1, except for ECHOs. See CV SAP for details.

Data management will ensure all assessments performed at the end of the feeder study and for which results are reused for Visit 1 are transferred to the Study 1900 database. If there is no non-missing assessment collected at Visit 1 for a variable (except for ECHOs), then the baseline value for the subject is missing.

7.6.2 Relative Day

Relative days for an event or measurement occurring before the reference date (date of first dose of study drug, assumed to be the same as date of Visit 1) will be preceded by a "-" and are calculated as follows:

Relative Day = (Event Date - Reference Date)

Relative days for an event or measurement occurring on or after the reference date (Visit 1 date) and up to and including the date of last dose in Study 1900 are calculated as follows:

Relative Day = (Event Date - Reference Date) + 1

For events or measurements occurring after the date of last dose of study drug (including tapering) in Study 1900 the relative day will be calculated with the date of last dose administration in Study 1900 as reference. Relative day in this case will be prefixed with "+" in the data listings and will be calculated as follows:

Relative Day = + (Event Date - Reference Date)

Note: relative day will be computed for fully reported dates only (for imputed dates it will not be computed). If date of last dose cannot be determined, it will be imputed as EOS/ET date + 8 days for subjects tapering off drug, and as EOS/ET date for any other subjects.

7.6.3 Open-label Extension (OLE) Treatment Period

The OLE Treatment Period covers the period during which subjects will receive open label treatment with ZX008 until approval of ZX008 has been obtained from regulatory authorities for the subject's indication and country of residence, until a managed access program is established, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first.

7.6.4 Post-dosing Period

For subjects discontinuing from study treatment and not transitioning to commercial drug, the Post-dosing Period begins immediately at the end of OLE Treatment Period defined by EOS/ET Study Visit and extends for a planned 2 weeks. This includes the Taper Period, if applicable to

the subject. The visit at the end of the Post-dosing Period is labelled "EOS/ET +14 days" in outputs.

7.6.5 Mean Daily Dose

The mean daily dose for a subject, sometimes referred to as the actual mean daily dose, is the average dose of ZX008 in mg/kg/day taken by a subject between Visit 1 and the EOS/ET Visit.

The calculation of the mean daily dose is based on the actual dose of ZX008 and takes into account dosing rules that capped the amount of drug that could be taken in a single day.

The mean daily dose of ZX008 per subject during the OLE is calculated from the weighted average of the assigned daily dosages by the investigator during the study, and the number of days the subject was maintained at each dose level.

The following categories will be used to describe mean daily dose and will be presented in mg/kg/day:

- 0 - < 0.4
- 0.4 - < 0.6
- ≥ 0.6

On each day, the actual dose will be calculated as:

1. Assigned dose level (mg/kg), if the subject's weight (kg) * assigned dose (mg/kg) was ≤ Maximum allowed dose or
2. 30 (mg) / weight (kg), if the subject's weight (kg) * assigned dose (mg/kg) was > Maximum allowed dose, if the subject was not on concomitant STP or
3. 20 (mg) / weight (kg), if the subject was on concomitant STP and the subject's weight (kg) * assigned dose (mg/kg) was > 20 mg.

The reasoning for this is that the maximum quantity to be given on any day is 30 mg for subjects not on concomitant STP and 20 mg for subjects on concomitant STP.

The mean daily dose of ZX008 per subject during the OLE will be calculated from the weighted average of the actual daily dosages and the number of days the subject remains on each actual dosage during the OLE Treatment Period.

More specifically, let $Dose_1$ be a subject's initial actual dosage in the OLE. The subject will be assumed to remain compliant on that dosage until there is a documented change in dosage assigned by the investigator or until the EOS/ET visit. Let $Days_1$ be the number of day that the subject is assumed to be on that initial actual dosage. If a new actual dosage, $Dose_2$, resulting either from a change in assigned dosage or from a relevant change in the body weight and/or STP treatment, the subject will be assumed to continue at that dosage for the total number of days, $Days_2$, until another change in actual dosage is documented or the subject reaches the EOS/ET visit.

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

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

where $Dose_n$ and $Days_n$ are the last assigned dosage and number of days spent on the last assigned dosage (up to and including the EOS/ET visit), respectively.

Special cases will be handled as follows:

- If baseline vital signs (body weight) assessment hasn't been performed, the data of the next available visit will be used.
- For subjects who terminate early but attend an ET visit, the calculation will assume subjects stayed on their last assigned dose from the time it was assigned until the time of the treatment termination date or ET visit, whichever is earlier.
- For subjects who are lost to follow up and do not have an EOS/ET visit, the calculation will be based on the dosages and time spent in OLE up to and including their last on-treatment visit.
- For subjects who are lost to follow up prior to Visit 2, the calculation will use the initial assigned dosage as the subject's mean daily dose.

Volume (ml) should not be used to calculate the mean daily dose as it may lead to discrepancies.

If it is not possible to determine a subject's mean daily dose due to a lack of data, an additional "Unknown" mean daily dose group will be added to summary tables and listings.

7.6.6 Modal Dose

For each subject, the ZX008 dose administered on the greatest number of days during the Treatment Period is the modal dose for that subject.

7.6.7 Study Completion

A subject will have completed the study when they have completed 36 months of treatment (24 months in Denmark) or have transitioned to commercial drug. A subject may continue in the study past 36 months of treatment if ZX008 has not yet been approved from regulatory authorities for the subject's indication and there is no managed access program available to the subject.

A subject will be considered to have completed 36 months of treatment (24 months in Denmark) if the EOS/ET visit (last on-treatment visit for subjects lost to follow-up without an EOS/ET visit) falls on Study Day 1050 or later (Study Day 690 or later in Denmark).

8 EFFECTIVENESS ASSESSMENTS

All effectiveness assessment analyses will be performed on the mITT Population. Results will be summarized in tables and presented in a subject listing. The summaries will be presented overall and by seizure disorder (Dravet syndrome or LGS) for the following visits: Months 6, 12, 18, 24, 30, 36, and Last On-Treatment Visit.

8.1 Improvement in Seizure Burden

Based on discussions with the parent/caregiver, clinical evaluation, and review of an optional seizure diary, the percent improvement in seizure burden will be assessed by the investigator using one of the following: <25%, ≥25%, ≥50%, ≥75%, 100% (i.e., seizure-free) improvement. The number and percentage of subjects in each of the 5 categories will be presented for each visit as compared to last visit. A two-sided 95% CI will be calculated for each percentage using the

Clopper-Pearson method. Figures will show the percentage of subjects in each category at each visit overall and by seizure disorder (Dravet syndrome or LGS).

Note that at the start of the current trial, most subjects will have already been receiving ZX008 for at least one year in an earlier, open-label trial, i.e., in a feeder study. Thus, the change in seizure burden in the current trial may not accurately reflect the full response to ZX008 treatment.

8.2 Clinical Global Impression – Severity & Improvement

As subjects entering Study 1900 have been treated in the prior open-label trial leading to some level of improvement, the CGI-Improvement score may show little movement (i.e., No Change).

The CGI-S questionnaire will be administered at Visit 1 to establish the baseline severity of disease and serve as a reference for assessing improvement over the course of the OLE. As above, subjects were treated with ZX008 prior to baseline for this trial, and the severity ratings at baseline may reflect previous clinical improvement. CGI-S assessments will be made independently by both the investigator and parent/caregiver. The CGI-S may be repeated at later visits if there is a permanent change in the person making the assessment.

The CGI-S comprises 4 ratings (refer to Appendix 3 of the Clinical Study Protocol Amendment 4.0). The severity of a subject's condition overall (Global), and for each of the 3 more specific indicators of health (cognition, behavior, and motor abilities) will be rated on a 7-point scale ranging from 1 (normal, not at all ill) to 7 (among the most extremely ill) as follows:

1=normal, not at all ill

2=borderline ill

3=mildly ill

4=moderately ill

5=markedly ill

6=severely ill

7=among the most extremely ill

CGI-S baseline characteristics will be included in the Demographics table. Specifically, the number and percentage of subjects in each of the 7 categories of the overall CGI-S score will be presented. Analogous statistics will be presented for the 3 more specific indicators of health in the CGI-S. The Enrolled Population will be used for baseline characteristics for CGI-S. If the rater changes during the study, a new CGI-S rating of severity at Baseline will be performed to be used for the subsequent CGI-I evaluations. CGI-S ratings after Baseline will be provided in a listing.

The CGI-I will be assessed at each visit beginning at Visit 2 (6 months, except for France: 3 months) through the end of study and permits a global evaluation of the subject's improvement over time. The investigator and the parent/caregiver (independently) will perform four ratings each, one for the subject's condition overall, and three for the more specific indicators of improvement, in cognition, behavior, and motor abilities (refer to Appendix 4 of the Clinical Study Protocol Amendment 4.0).

The improvement of a subject's condition overall, and for each of the 3 more specific indicators of improvement (cognition, behavior, and motor abilities), 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 investigator and the parent/caregiver each indicate the appropriate response that adequately describes how the subject's overall condition has improved or worsened relative to the CGI-S rating provided at baseline.

Frequency tables will be produced for each time point and will include the number and percentage of subjects rated in each category, along with an associated Clopper-Pearson two-sided 95% CI.

Separate tables reflecting the ratings by the investigator and the parent/caregiver will be presented.

Figures will show the percentage of subjects in each category will be presented at each visit, overall and by seizure disorder (Dravet syndrome or LGS), for both ratings by the investigator and the parent/caregiver.

Categorical and subgroup presentations of CGI-I analysis may include:

- Categories:

  Clinically meaningful improvement (1, 2)

  Improved (Score = 1, 2, 3)

  Improved or No Change (Score = 1, 2, 3, 4)

- Domains:

  Global

  Cognition

  Behavior

  Motor Abilities

- Age groups:

  2 - < 6 years

  6 - < 12 years

  12 - < 18 years

2 - < 18 years

≥ 18 years

- Sex:

  Male

  Female

- Number of prior and concomitant antiepileptic medications used:

  ≤ 2

  3

  ≥ 4 medications

The number of prior and concomitant antiepileptic medications used is defined as the number of unique different medications started prior to Visit 1 and ongoing at Visit 1 where the Anatomical Therapeutic Chemical (ATC) Level 2 code is "Antiepileptics". Different medications are those with different standardized medication names.

The global CGI-I score will also be summarized by subjects' CGI-S score obtained at Visit 1. Note that the CGI-S score obtained at Visit 1 should be used even if there is a more recent CGI-S score recorded. These summaries will not be presented by mean daily dose. For these summaries subjects will be aggregated into 1 of 3 categories based on CGI-S score:

- CGI-S = 1 or 2 (normal or borderline ill)
- CGI-S = 3 or 4 (mildly or moderately ill)
- CGI-S = 5, 6, or 7 (markedly, severely, or among the most extremely ill).

The relationship between global CGI-I in the current study and degree of improvement seen in the CGI-I feeder study will also be investigated. Tables will be produced that summarize CGI-I in the current study by subjects' CGI-I Global rating at the end of the feeder study and will be reported overall and by seizure disorder (Dravet syndrome or LGS). These summaries will not be presented by mean daily dose.

Individual subject data will be listed for the CGI-I scales as assessed by the investigator and parent/caregiver.

9 SAFETY ASSESSMENTS

Additional safety summaries may be produced by seizure disorder (Dravet syndrome or LGS) if warranted.

9.1 Disposition of Subjects

Disposition of all subjects in the SAF population will be summarized in a table overall and by seizure disorder (Dravet syndrome or LGS). The following information will be included: numbers and percentages of subjects who completed 12 months, 24 months, 36 months, or greater than 36 months of treatment, as appropriate; numbers and percentages of subjects who completed the study; and the numbers and percentages of subjects who discontinued the study

and reasons for discontinuation. In addition to the EOS/ET Visit, completion of additional visits, such as the EOS/ET Follow Up Visit, may also be presented in the table.

The number and percentage of enrolled subjects included in each analysis population will be summarized in a table.

The completion status and reasons for the study and treatment discontinuation of subjects in the Enrolled population will be listed. Classification to analysis populations will also be presented in a listing by subject.

9.2 Demographics and Other Baseline Characteristics

Subject demographics and seizure disorder (Dravet syndrome or LGS) data will be collected at study entry.

A table will summarize demographics and baseline characteristics for the SAF Population overall and by seizure disorder (Dravet syndrome or LGS).

The following demographic and baseline characteristics will be summarized:

- Seizure disorder
- Feeder study
- Age in years at Visit 1
- Sex
- Race
- Ethnicity
- Height (cm) at Visit 1
- Weight (kg) at Visit 1
- BMI (body mass index) (kg/m^2) at Visit 1
- Region: North America (including United States of America [USA], Canada, Mexico), Europe, and Australia.
- Country

Age in years at Visit 1 will be recalculated as (date of Visit 1)-(date of birth)/365.25 for the continuous summary of age.

The CGI-S ratings by Investigator and by parent/caregiver will be summarized by subgroups (age, sex, and number of prior and concomitant antiepileptic medications used) separately from other demographics and baseline characteristics data using the Enrolled Population overall and by seizure disorder (Dravet syndrome or LGS).

The age categories used in the demographics table are:

- 2 - <6 years
- 6 - <12 years
- 12 - <18 years

- 2 - <18 years
- >=18 years

Additionally, the age categories required by EudraCT and clinicaltrials.gov will be used in the demographics table.

All subject demographic data will be listed for the Enrolled Population.

9.3 Medical History and Ongoing Diseases and Conditions

All subjects in the SAF Population who had prior medical history as per the CRF, will be listed by subject including subject number, description of the disease/condition, Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), MedDRA preferred term (PT), start date, and stop date (or ongoing if applicable). Additionally, subjects' medical history from prior studies will be carried over and ongoing AEs from the prior studies will be considered medical history unless there is an increase in the frequency or severity of the condition from the prior study, after the first dose of ZX008 in Study 1900 (assumed to be taken on Visit 1 date). In addition, any new clinically significant medical condition that occurred in prior studies will be entered as medical history.

AEs that occur after signing the ICF for this study, but before Visit 1 will be recorded as AEs in the prior study and medical history in Study 1900.

A medical history table will be produced for the SAF Population, displaying the number and percentage of subjects with any previous and ongoing medical history conditions by SOC and PT.

All medical history conditions and ongoing diseases and conditions will be coded using Version 21.1 or later of MedDRA.

A glossary of all medical history and ongoing diseases and conditions terms will be presented for the SAF Population. All medical history and ongoing diseases and conditions data will be listed for the SAF Population.

9.4 Epilepsy History

Seizure history may be recorded at Visit 1 and will be listed by seizure disorder (Dravet syndrome and LGS).

9.5 Procedures

Procedures (prior and concomitant non-medications, surgical history and concomitant procedures) will be listed for the SAF Population.

9.6 Physical and Neurological Examinations

Abbreviated physical and neurological examinations will be performed at Day 1 (Visit 1) and every 6 months thereafter as clinically indicated, as well as at the EOS/ET visit, the Follow-up visit (EOS/ET + 14 days) depending on last exam and AEs, and the Cardiac Follow-up visit (last dose + 6 months). Abbreviated physical and neurological examinations will also be performed at EOS/ET + 3 months and EOS/ET + 24 months in France, and at EOS/ET + 12 months in the UK. A full examination may be performed if warranted.

Listings based on the SAF will be presented showing results from abbreviated physical and neurological examinations, for example if any abnormal findings and any clinically significant abnormal findings were present.

9.7 Vital Signs, Weight and BMI

Vital signs data are scheduled to be documented at each clinic visit according to the Schedule of Assessments for Subjects (refer to Section 16.1 of this SAP, Amendment 4.0, Amendment 4.1-FR, Amendment 4.1-UK tables). Vital sign measurements will include blood pressure, heart rate, temperature, and respiratory rate and observed values and changes from Baseline will be summarized and reported in tables for the SAF population.

Body weight and height are scheduled for collection at each clinic visit according to the Schedule of Assessments for Subjects (refer to Section 16.1 of this SAP, Amendment 4.0, Amendment 4.1-FR, and 4.1-UK tables). BMI will be recalculated during programming as weight (kg) / height $(m)^2$.

Age and sex-based z-scores for height and weight at each assessment will be determined using growth charts available from the Centers for Disease Control (CDC) and the World Health Organization (WHO). Details of the data sources are available at the following website, updated 09Jan2023.

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

The Z-scores will be determined based on the subject's age in months at the date of assessment. For subjects with an incomplete birth date due to country requirements, January 1st of the provided year of birth will be assumed to be the date of birth. Age (in months) will be recalculated at each visit as [(date of visit) - (date of birth)]*12/365.25 for the calculation of z-scores. The z-scores will be determined only for subjects whose age at assessment is ≤ 20 years of age. Z-scores will be included in selected tables overall and split by syndrome (Dravet syndrome or LGS).

For weight the occurrence of at least a ≥ 7% gain/reduction or ≥ 10% gain/reduction from Baseline will be summarized in tables and reported for the SAF Population (overall and split by syndrome) by visit and at any time during the study.

Spaghetti plots will be used to summarize changes in weight. Plots of z-scores will be produced for each subject with a ≥ 7% and ≥ 10% change from Baseline in weight and will be displayed by visit.

For each vital signs, height, weight, and BMI parameter, observed values at each visit and change from baseline at each post-baseline visit will be summarized with descriptive statistics in a table for the SAF Population.

Listings of the markedly abnormal vital signs, weight, and BMI results will be provided by syndrome (Dravet syndrome or LGS). Markedly abnormal values are summarized in the table below:

Parameter	**Age Group** (Years)	**Abnormally** Low	**Abnormally** High	**Change Criteria**
Weight (kg)	All			≥7% reduction/gain from baseline
	All			≥10% reduction/gain from baseline
Heart Rate (beats /minute)	2	< 87	> 150	Absolute Change from baseline > 20 bpm
	3	< 82	> 146	Absolute Change from baseline > 20 bpm
	4-5	< 77	> 142	Absolute Change from baseline > 20 bpm
	6-7	< 71	> 137	Absolute Change from baseline > 20 bpm
	8-11	< 66	> 129	Absolute Change from baseline > 20 bpm
	12-14	< 61	> 121	Absolute Change from baseline > 20 bpm
	15-17	< 57	> 115	Absolute Change from baseline > 20 bpm
	18-100	< 60	> 100	Absolute Change from baseline > 20 bpm
SBP (mmHg)	2-4	< 85	> 100	Absolute Change from baseline > 20 mmHg
	5-11	< 90	> 110	Absolute Change from baseline > 20mmHg
	12-17	< 100	> 120	Absolute Change from baseline > 20 mmHg
	18-100	< 90	>130	Absolute Change from baseline > 20 mmHg

Parameter	**Age Group** (Years)	**Abnormally** Low	**Abnormally** High	**Change Criteria**
DBP (mmHg)	2-4	< 40	> 64	Absolute Change from baseline > 10 mmHg
	5-11	< 51	> 75	Absolute Change from baseline > 10 mmHg
	12-17	< 61	> 80	Absolute Change from baseline > 10 mmHg
	18-100	< 60	> 85	Absolute Change from baseline > 10 mmHg
BMI (kg/m^2)	2-17	≤ 20	≥ 25	
	18-100	≤ 20	≥ 30	
Respiration Rate (breaths/min)	2	< 18	> 42	
	3	< 18	> 40	
	4-5	< 17	> 37	
	6-7	< 16	> 35	
	8-11	< 15	> 31	
	12-14	< 13	> 28	
	15-17	< 13	> 26	
	18-100	< 12	> 20	
Temperature (Celsius)	All	≤ 36	≥ 38	> 4

Vital signs, weight, height, z-scores, and BMI data will be presented for the SAF Population in a listing. Electrocardiogram and ECHO Analysis of ECGs and Doppler ECHOs will be included in a separate CV SAP from ERT (formerly Biomedical Systems).

9.8 Chest x-ray (subjects in France and Netherlands only)

For subjects enrolled in the Netherlands, an anterior/posterior chest x-ray will be performed at Visit 1 and Visit 13 (EOS/ET), and as clinically indicated at visits V3, V5, V7, V9, V11. For

subjects enrolled in France, chest x-ray will be required every 6 months, at clinic visits V2, V4, V6, V8, V10, V12, and will be assessed as clinically indicated at clinic visits V1, V3, V5, V7, V9, V11, V13. Subjects in France will have additional chest x-rays 3 months and 24 months after study completion and subjects in Netherlands will have additional chest x-rays 24 months after study completion.

Results will be listed using the SAF Population.

9.9 Electroencephalogram (subjects in Italy only)

For subjects enrolled in Italy, an electroencephalogram (EEG) will be performed at Visits 1 to 7 as clinically indicated. Abnormal clinically significant findings are reported as adverse events.

Results will be listed using the SAF Population.

9.10 Columbia-Suicide Severity Rating Scale (C-SSRS)

C-SSRS data will be collected at each clinic visit as indicated in the Schedule of Assessments (refer to Section 16.1). 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.

Subject C-SSRS data will be listed using the SAF Population only for those subjects who reported any suicidal ideation, suicidal behavior or self-injurious behavior without suicidal intent.

Suicidal Ideation:

The following outcomes are C-SSRS categories for suicidal ideation and have binary responses (yes/no):

[redacted]

A positive response to one or more of the suicidal ideation questions is assessed as a “yes” answer at any time during the OLE treatment period to any one of the five questions (1-5) above.

Suicidal Behavior:

The following outcomes are C-SSRS categories for suicidal behavior and have binary responses (yes/no):

[redacted]

[redacted]

A positive response to one or more of the suicidal behavior questions is assessed as a "yes" answer at any time during the OLE treatment period to any one of the six questions (6-11) above.

A positive response to the self-injurious behavior without suicidal intent endpoint is a "yes" response at any time during the OLE treatment period to the respective C-SSRS question as per the C-SSRS scoring manual.

Data will be summarized in tables including the number of Subjects with a "Yes" Response to Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior Without Suicidal Intent at Baseline in Study 1900 and post-baseline during the OLE treatment period, and shift tables from baseline to during the OLE treatment period.

9.11 Concomitant Medications

Medication start and stop dates will be compared with the Visit 1 date to allow medications to be classified as either prior only, prior and concomitant, or concomitant only. Medications that stopped on or prior to Visit 1 are classed as prior only. Medications that began prior to Visit 1 and were ongoing at Visit 1 are both prior and concomitant. Medications that began on or after Visit 1 are concomitant only.

Medications will be summarized in tables and listed by subject in the SAF Population and will include the following information: reported name, whether it was a rescue medication, PT, ATC category, the route of administration, dose, frequency, start and stop date, and indication.

Medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) (Version Sept 1, 2018 Global) and will be classified by ATC categories.

If medication start dates are missing or partial, the dates will be compared as far as possible with the date of Visit 1. The medication will be assumed to be concomitant unless there is clear evidence to suggest that the medication stopped prior to Visit 1. See Section 7.5.1 for complete rules on date imputation for medications.

Three summaries of medications will be produced: one for medications and therapies/treatments classified as prior only, one for medications and therapies/treatments classified as both prior and concomitant, and one for medications and therapies/treatments classified as concomitant only. Medications and therapies/treatments will be summarized for the SAF Population and sorted alphabetically by ATC categories (Level 1: Anatomical main group and Level 2: pharmacological/therapeutic subgroup) and WHO-DD drug code. For each medication, the number and percentage of subjects will be displayed. These three summaries will be repeated for AEDs only (defined as ATC Level 2 category = "Antiepileptics"). Summaries for prior and concomitant and concomitant medications only will be produced overall and by syndrome (Dravet syndrome and LGS). Summaries for prior medications will be produced for all seizure disorders combined.

Plasma concentrations of concomitant AEDs will be listed by subject.

9.12 Treatment Exposure / Compliance

9.12.1 Mean Daily Dose

The mean daily dose for a subject, sometimes referred to as the actual mean daily dose, is the average dose of ZX008 in mg/kg/day taken by a subject over the entire course of Study 1900.

Subjects who enter Study 1900 from either Study 1503 or Study 1601 Part 2 will initially receive ZX008 at the dosage assigned at the last visit in those trials. The starting dosage for subjects entering this study from another Zogenix-sponsored clinical study of ZX008 will be determined through consultation between the investigator and CRO Medical Monitor. Investigators may increase or decrease the assigned dosage during the OLE.

The calculation of the mean daily dose is based on the actual dose of ZX008 taken during the OLE not including the Taper Period and takes into account dosing rules that capped the amount of drug that could be taken in a single day.

9.12.2 Treatment Exposure

Treatment exposure for a subject is defined as:

- (Date of last dose) – (Date of first dose) + 1

and is recorded in days. Date of first dose is assumed to be the date of Visit 1. If date of last dose cannot be determined, it will be imputed as EOS/ET date + 8 days for subjects tapering off drug, and as EOS/ET date for any other subjects.

Treatment exposure can be converted to months or years as follows:

- 1 month = 30 days
- 1 year = 12 months = 360 days

Exposure will be summarized on the SAF Population continuously and for the following time periods: < 6 months, 6 months - < 1 year, 1 - < 2 years, 2 - < 3 years, ≥ 3 years. Summaries will be produced overall and by syndrome (Dravet syndrome and LGS).

Cumulative exposure will be reported categorically on the SAF Population for the following time periods: > 0 months, ≥ 6 months; ≥ 1 year, ≥ 2 years, and ≥ 3 years. Summaries will be produced for all seizures disorders combined only.

Total study treatment exposure in subject-years is defined as the sum over all subjects of:

- [(Date of last dose) – (Date of first dose) + 1]/360

or the sum over all subjects of (treatment exposure/360) and is recorded in years. This will be reported on the SAF Population. Summaries will be produced overall and by syndrome (Dravet syndrome and LGS).

9.12.3 Compliance

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

Compliance will be estimated based on the amount calculated to be consumed, determined using the weight of the dispensed bottles and weight of the returned bottles. The calculation is performed by subtracting the weight of all returned bottles from the weight of all dispensed bottles through up until EOS/ET (last on-treatment visit for subjects lost to follow-up), not including bottles dispensed for tapering, and divide this difference by the number of days between first dispensed and last returned day. Missing values will not be taken into account.

Compliance will be summarized for the SAF Population and reported in tables according to mean daily dose categories.

Compliance values will be categorized as:

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

9.13 Adverse Events (AEs)

An AE is any untoward medical occurrence (including an abnormal, clinically significant laboratory finding) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. AEs are categorized by the investigator as related or unrelated to study drug. If the AE is thought to be, probably or possibly related to study drug, then it is categorized as related. Abnormal clinically significant observations will be reported as AEs.

The original terms used by the investigators in the CRFs to identify AEs will be coded using the MedDRA Version 21.1 or later.

Adverse events will be summarized in tables for the SAF Population. Adverse events will be listed by subject for the Enrolled Population.

9.13.1 Severity of Adverse Events

The severity of AEs (whether nonserious or serious AEs) is to be assessed by the investigator as follows:

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 subject.

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

In tables, any AE with missing severity will be imputed as "severe" and any AE with missing relationship to study medication will be imputed as "related".

9.13.2 Treatment-Emergent Adverse Events (TEAEs)

A treatment-emergent adverse event (TEAE) is defined as:

An adverse event that begins on or after the first day of treatment with ZX008 in Study 1900 or that occurs prior to first ZX008 treatment in Study 1900 but increases in severity after treatment in Study 1900 begins. Thus, events recorded at Follow-up or Cardiac Follow-up will be considered treatment-emergent.

For results disclosure on public registries (e.g., ClinicalTrials.gov), only TEAEs will be summarized for the primary objective.

The number and percentage of subjects with at least one of the following events will be summarized in an overall summary table, including the number of events of each type:

- TEAE
- Treatment-related TEAE
- Serious TEAE
- Treatment-related serious TEAE
- Severe TEAE
- TEAE leading to permanent discontinuation of study treatment
- TEAE leading to permanent discontinuation from the study
- All deaths (AEs leading to death)
- Deaths (TEAEs leading to death)

This overall summary table will be presented for the SAF Population for all subjects and for Dravet syndrome and LGS separately. The summary will be presented by mean daily dose categories and by modal daily dose categories. The same dose categories will be used for both mean and modal daily dose.

For the TEAE categories listed below, tables of the number and percentage of subjects summarized by SOC and PT will be presented for the SAF Population. For All TEAEs, Serious TEAEs and TEAEs leading to permanent discontinuation of study treatment only, the incidence of TEAEs will be summarized by modal dose as well as mean daily dose, and for all subjects and for Dravet syndrome and LGS separately. These tables will be sorted by alphabetical SOC and then by decreasing frequency of PTs among all subjects in the study.

- All TEAEs
- Serious TEAEs

- Treatment-related TEAEs
- All TEAEs leading to permanent discontinuation of study treatment
- All TEAEs leading to permanent discontinuation from the study
- All TEAEs leading to death
- Non-serious TEAEs above reporting threshold of 5% of subjects (in any mean daily dose group or overall)
- Non-serious TEAEs above reporting threshold of 5% of subjects (overall)
- TEAEs by maximum severity
- TEAEs by maximum relationship to study treatment
- Serious TEAEs by relationship to study treatment
- Fatal TEAEs by relationship to study treatment

For the summary of TEAEs by maximum severity, if more than one event occurred with the same PT for the same subject, then the subject will be counted only once by the maximum severity level of that PT. Similarly for the summarization of TEAEs by maximum relationship, if more than one event occurred with the same PT for the same subject, then the subject will be counted only once by the maximum relationship of that PT.

A summary of the most frequently occurring non-serious TEAEs (>5%) in any mean daily dose group will be presented, and a separate summary will be presented of the most frequently occurring non-serious TEAEs (>5%) in the overall column only.

Summaries of TEAEs and treatment-related TEAEs will be provided for the following subgroups:

- Sex: Male, Female
- Age (at Visit 1): 2– <6 years, 6–<12 years, 12 - <18 years, ≥ 18 years
- Concomitant valproate use: Yes, No

For the summaries of subjects who used valproate (valproate magnesium, valproate sodium, valproate semisodium, ergynyl chrono, and other PTs) versus those who did not during the study, an updated list of valproates will be provided before the final analysis.

Additional summaries may be produced of TEAEs and treatment-related TEAEs for subgroups of other concomitant medications if warranted.

A summary of exposure-adjusted incidence rate of TEAEs will be presented by SOC and PT in the SAF population, with the incidence rate being calculated as:

(number of subjects who experienced the particular TEAE)/ (total treatment exposure in 100 subject-years)

where 1 subject-year = 360 days of treatment exposure.

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

The following listings will be produced (events considered to be TEAE will be identified in the listing):

- All AEs
- SAEs
- AEs that lead to premature discontinuation from study or treatment
- Deaths

9.13.3 Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically significant.

The presentation of SAEs is described in Section 9.13.2.

9.14 Clinical Laboratory Evaluation

Laboratory safety parameters were collected if clinically indicated, and if so, analyzed by a central laboratory using standard validated methods. Parameters to be assessed will be at the discretion of the investigator.

The following parameters may be assessed:

- 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), aspartate aminotransferase (AST; SGOT), bicarbonate, blood urea nitrogen (BUN), calcium (Ca), chloride (Cl), creatinine, creatine kinase, gamma-glutamyl transferase (GGT), globulin, glucose, lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total bilirubin, direct bilirubin, total cholesterol, total protein, triglycerides, uric acid
- Urine or serum pregnancy test: Pregnancy testing will be performed at each visit in female subjects of childbearing potential.

Markedly abnormal laboratory results are results that are flagged as critical high (CH) or critical low (CL) (or notable high (NH) or notable low (NL) for variables where 'notable' flags were used instead of 'critical' flags) in the laboratory database.

Hematology, clinical chemistry, and pregnancy test results will be listed by subject and study time point. Markedly abnormal laboratory values will also be listed for hematology and clinical chemistry by syndrome (Dravet syndrome or LGS), subject and study time point. All values

outside the clinical reference ranges will be flagged in these listings. Values will be flagged as low (RL) if below the lower limit of the reference range and high (RH) for values above the upper limit of the reference range (or CL/NL if below the lower critical/notable limit and CH/NH if above the upper critical/notable limit).

Values recorded as <X or >Y (where X and Y are typically lower and upper limits of quantification, respectively) will be replaced by X or Y for the calculation of descriptive statistics (observed values and changes from Baseline).

Summary tables of observed values and changes from Baseline for the SAF Population will be created for each laboratory parameter by visit. Additional exploration of the data may be conducted as warranted.

Pregnancy testing data will be listed for the SAF population.

10 INTERIM ANALYSES

A formal interim analysis took place with a data cut of 19 October 2020. All subject data (EDC, endpoint data, laboratory safety parameters, etc.), from any source, up to and including that date was used in the interim analysis. A subset of the full study TFLs was used for the interim analysis. An interim analysis of Study 1900 was performed to generate data summaries needed for marketing applications to support the use of ZX008 in the treatment of seizures associated with LGS in children and adults. Only subjects with LGS were included in the interim analysis.

The SAF Population was used for the interim safety analysis.

The mITT Population was used for the interim effectiveness analysis.

The sample size for the interim analysis was not statistically determined.

The safety endpoints of the interim analysis were:

- AEs
- Laboratory safety (hematology, chemistry)
- Vital signs (blood pressure, heart rate, temperature, and respiratory rate)
- ECGs
- Doppler ECHOs
- Body weight/height
- Chest x-ray (subjects in France and Netherlands only)
- C-SSRS

Any AE with missing severity at the time of the interim analysis was tabulated and listed as "missing."

Laboratory safety parameters (hematology, chemistry) and physical/neurological examinations will only be assessed as clinically indicated. In all countries except France, ECGs will only be assessed as clinically indicated. In France, only the ECGs at clinic visits 1 and 13 and chest x-rays at clinic visits 3, 5, 7, 9, and 11 will be assessed as clinically indicated; these assessments are required at the other clinic visits. Further, chest x-rays were collected only in France and NL,

and in the latter, only when clinically indicated. EEGs were collected only in Italy, and only when clinically indicated.

As subjects entering Study 1900 have been treated to some level of improvement in the prior open-label trial, the CGI-Improvement score may show little movement (i.e., No Change).

The effectiveness endpoints of the interim analysis were:

- Percent improvement in seizure burden since last visit as assessed by the investigator (or designee)
- CGI-I, globally and for specific domains, as assessed by investigator (or designee)
- CGI-I, globally and for specific domains, as assessed by parent/caregiver

11 DAY 120 SAFETY UPDATE

A Day 120 safety update occurred with a data cut of 02 August 2021. All subject data (EDC, subject diary, laboratory safety parameters, etc.) up to and including that date was used in the analysis for subjects with LGS only.

A subset of the full study TFLs was used for the analysis and the populations used for the 120-day safety update and they are as follows:

- Table of Change in Seizure Burden (<25%, >=25%, >=50%, >=75%, 100% Improvement) Since Previous Assessment -LGS mITT Population

Table of Clinical Global Impression –Improvement (CGI-I) Global Rating by Investigator -LGS mITT Population and

- Table of Clinical Global Impression –Improvement (CGI-I) Global Rating by Parent / Caregiver - LGS mITT Population
- Figure of Distribution of CGI-I Rating by Investigator -Percentage of Subjects in Each Category by Month -LGS mITT Population and
- Figure of Distribution of CGI-I Rating by Parent/Caregiver -Percentage of Subjects in Each Category by Month -LGS mITT Population
- Listing of Subjects Who Achieved <25%, >=25%, >=50%, >=75% or 100% Improvement in Seizure Burden (LGS mITT Population)
- Listing of Clinical Global Impression – Improvement Rating Individual Subject Data (LGS mITT Population).

Only subjects who transitioned into Study 1900 from Study 1601 Part 2 were included in the 120-day safety analysis.

12 CHANGES TO METHODS PLANNED IN THE PROTOCOL

12.1 Changes in the Study Population

No Japanese patients will be enrolled in Study 1900.

12.2 Changes in the Analysis Populations

The Enrolled Population was added for use in summary tables and listings.

The Per Protocol Population was removed from the Analysis Populations as Study 1900 focuses on safety rather than efficacy endpoints and therefore will not be used in any planned analysis.

13 INDEPENDENT DATA AND SAFETY MONITORING COMMITTEE (IDSMC)

A safety oversight monitoring plan will be in place with an IDSMC evaluating data from the subjects. 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 oversight of safety and IDSMC responsibilities can be transferred back to the Sponsor's representative/study physician at any time.

The following listings will be provided, from time to time, to aid the IDSMC in monitoring the study:

- Demographics
- Visit Type
- Medical History
- Seizure History Dravet syndrome
- Seizure History LGS
- Seizure History of other epileptic disorders
- Concomitant Medications
- Rescue Medications
- Dose Changes
- Adverse Events
- Serious Adverse Events
- Vital Signs
- Physical and Neurological Examinations
- Central Laboratory Assessments
- ECG
- Seizure Assessments
- C-SSRS Since Last Visit
- ECHOs
- End of Treatment
- Study Exit

14 CLINICAL TRIAL REGISTRY OUTPUTS

The following tables outlined in previous sections of the SAP fulfil the criteria for transparency reporting for Clinical Trial Registries (clinicaltrials.gov and EudraCT):

Table 1: CTR Outputs

Standard Shell	Title	Analysis Population	Comments
DS_T_03	Disposition and Discontinuation Reasons	SAF	Refer to Section 9.1.
DM_T_01	Demographics	SAF	Refer to Section 9.2. Note: all age categories are mandatory.
AE_T_01	Incidence of TEAEs – Overview	SAF	Refer to Section 9.13.2. Note: this is mandatory, including all deaths and TEAEs leading to deaths.
AE_T_06	Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% of Subjects	SAF	Refer to Section 9.13.2.
DS_T_04	Discontinuation due to AEs*	SAF	*For small studies in populations where these events are not expected then the study team may utilize the lines from AE_T_01. The zeros in the relevant lines are sufficient for the Clinical Trial Registry (CTR) reporting. However, if an event is observed then the relevant table must be produced by CTR reporting.
AE_T_04b	Incidence of serious TEAEs by Relationship*	SAF	
AE_T_04b	Incidence of fatal TEAEs by Relationship*	SAF	

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16 APPENDICES

16.1 Schedule of Assessments

Protocol Amendment 4.0 (22 September 2022)

Table 2: Schedule of Assessments for Subjects (All Countries except Denmark, France, UK)

Study Assessments		**OLE Treatment Period***		**Follow-up**	**Cardiac Follow-up**
Visit Number	**Visit 1[a]**	**Visits 2, 3, 4, 5, 6 (Months 6, 12, 18, 24, 30)**	**Visit 7 (EOS/ET) Month 36**	**Visit 8 EOS/ET+ 14 days**	**Visit 9[h] last dose + 6 months**
Study Day	**1[a]**	**180, 360, 540, 720, 900 (window: ±7 days)**	**1080 (window: ±7 days)**	**14 days after EOS/ET**	**6 months post last dose**
Informed Consent	X[a]				
Entry Criteria Review	X				
Demographics	X				
Epilepsy History	X				
Abbreviated Physical/Neurological Examination	X[b]	X[f]	X	X[m]	X
Vital signs	X	X	X		
Weight, Height, BMI	X[i]	X	X	X	
ECG[b,c]	X	X	X		X
Doppler ECHO[d]	X	X	X		X

Study Assessments		**OLE Treatment Period***		**Follow-up**	**Cardiac Follow-up**
Visit Number	**Visit 1[a]**	**Visits 2, 3, 4, 5, 6 (Months 6, 12, 18, 24, 30)**	**Visit 7 (EOS/ET) Month 36**	**Visit 8 EOS/ET+ 14 days**	**Visit 9[h] last dose + 6 months**
Study Day	**1[a]**	**180, 360, 540, 720, 900 (window: ±7 days)**	**1080 (window: ±7 days)**	**14 days after EOS/ET**	**6 months post last dose**
Chest x-ray (France and Netherlands only)[b, e]	X	X	X		X
EEG (Italy only)[b, c, i]	X	X	X		
Pregnancy Test[g]	X	X	X		
Clinical laboratory evaluation (hematology/clinical chemistry)	X[b]	X[f]	X[f]		
Plasma sample for background AEDs		X[f]	X[f]		
C-SSRS	X	X	X		
Investigator CGI-Severity Rating (reference baseline)	X				
Parent/Caregiver CGI-Severity Rating (reference baseline)	X				
CGI-I (assessed by parent/caregiver)		X	X		

Study Assessments		**OLE Treatment Period***		**Follow-up**	**Cardiac Follow-up**
Visit Number	**Visit 1[a]**	**Visits 2, 3, 4, 5, 6 (Months 6, 12, 18, 24, 30)**	**Visit 7 (EOS/ET) Month 36**	**Visit 8 EOS/ET+ 14 days**	**Visit 9[h] last dose + 6 months**
Study Day	**1[a]**	**180, 360, 540, 720, 900 (window: ±7 days)**	**1080 (window: ±7 days)**	**14 days after EOS/ET**	**6 months post last dose**
CGI-I (assessed by investigator)		X	X		
Overall change in seizure frequency (assessed by investigator)	X	X	X		
Study Medication	D	C/R/D[k]	C/R/D	C/R	
Seizure Diary	R (if applicable)[l]	R (if applicable)	R (if applicable)		
Concomitant Medications	X[j]	X	----------X----------		
Adverse Events	X[j]	X	----------X----------		

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

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

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

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

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

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

e:In France and Netherlands only. Subjects in France and Netherlands will have an additional chest x-ray 24 months after study completion.
f: As clinically indicated. A full physical and/or neurological examination may be performed, if warranted. Abnormal clinically significant observations must be reported as adverse events.
g:Females of child-bearing potential
h:For subjects who discontinue treatment and do not continue with commercially available ZX008, a follow-up ECHO, and physical examination will be performed 6 months after study completion or early termination. Subjects in the United Kingdom will have an additional follow-up 12 months after study completion; subjects in France, Germany, and Netherlands will have an additional follow-up 24 months after study completion.
i: In Italy only.
j: Ongoing medications and ongoing adverse events should be captured in the CRF.
k:At the Principal Investigators discretion Study Drug can be collected/reviewed/dispensed at 3-month intervals.
l: Seizure Diary from core study to be reviewed, if applicable.
m:As appropriate based on last exam and reported AEs.

Country-specific Protocol Amendment 4.1 for France (22 September 2022)

Table 3: Schedule of Assessments for Subjects (France only)

Study Assessments	OLE Treatment Period*				Follow-up	Cardiac Follow up
Visit Number	**Visit 1[a]**	**Visits 2, 4, 6, 8, 10, 12 (Months 3, 9, 15, 21, 27, 33)[b]**	**Visits 3, 5, 7, 9, 11 (Months 6, 12, 18, 24, 30)**	**Visit 13 (EOS/ET) Month 36**	**Visit 14 EOS/ET+1 4 days**	**Visit 15/16/17[i] EOS/ET + 3, 6 and 24 months**
Study Day	**1[a]**	**90, 270, 450, 630, 810, 990 (window: ±7 days)**	**180, 360, 540, 720, 900 (window: ±7 days)**	**1080 (window: ±7 days)**	**14 days after EOS/ET**	**3, 6 and 24 months post last dose**
Informed Consent	X[a]					
Entry Criteria Review	X					
Demographics	X					
Epilepsy History	X					
Abbreviated Physical/Neurological Examination	X[b]		X[f, k]	X	X[n]	X
Vital signs	X		X	X		
Weight, Height, BMI	X	X	X	X	X	
ECG[d]	X	X[b]	X	X		X
Doppler ECHO[e]	X	X	X	X		X[d]
Chest x-ray (France and Netherlands only)[f]	X	X[b]	X[c,d]	X		X[f]
EEG (Italy only)[c,d, j]	X		X	X		
Pregnancy Test[h]	X		X	X		
Clinical laboratory evaluation (hematology/ clinical chemistry)	X[c]		X[g]	X[g]		
Plasma sample for background AEDs			X[g]	X[g]		
C-SSRS	X		X	X		
Investigator CGI-Severity Rating (reference baseline)	X					

Study Assessments	**OLE Treatment Period***				**Follow-up**	**Cardiac Follow up**
Visit Number	**Visit 1[a]**	**Visits 2, 4, 6, 8, 10, 12 (Months 3, 9, 15, 21, 27, 33)[b]**	**Visits 3, 5, 7, 9, 11 (Months 6, 12, 18, 24, 30)**	**Visit 13 (EOS/ET) Month 36**	**Visit 14 EOS/ET+1 4 days**	**Visit 15/16/17[i] EOS/ET + 3, 6 and 24 months**
Study Day	**1[a]**	**90, 270, 450, 630, 810, 990 (window: ±7 days)**	**180, 360, 540, 720, 900 (window: ±7 days)**	**1080 (window: ±7 days)**	**14 days after EOS/ET**	**3, 6 and 24 months post last dose**
Parent/Caregiver CGI-Severity Rating (reference baseline)	X					
CGI-I (assessed by parent/ caregiver)			X	X		
CGI-I (assessed by investigator)		X	X	X		
Overall change in seizure frequency (assessed by investigator)	X	X	X	X		
Study Medication	D	C/R/D	C/R/ D[l]	C/R	C/R	
Seizure Diary	D	R (if applicable)[m]	R (if applicable)	R (if applicable)		
Concomitant Medications	X[k]	X	----------X----------			
Adverse Events	X[k]	X	----------X----------			

BMI=body mass index; C=Collect; CGI-I=Clinical Global Impression-Improvement; D=Dispense; ECG=electrocardiogram; EOS=end of study; ET=early termination.
R=Review
*: Subjects will receive ZX008 treatment in this study until approval of ZX008 has been obtained from regulatory authorities for the subject's indication, until a managed access program is established as allowed per country-specific requirements in addition to legal and regulatory guidelines in the subject's country of residence, or until the investigational product development for the subject's indication is stopped by the Sponsor, whichever comes first. In that regard, participation could be extended beyond 36 months if none of the conditions above mentioned are met.
a:Assessments conducted at the End of Study Visit of 1503, 1601 Part 2, or other Zogenix protocol as applicable will be used for Visit 1 of this Protocol. Continuation of treatment in this study should be discussed at the start of the visit, at latest. For subjects who wish to continue, informed consent/assent must be obtained before conducting any assessments or distributing study drug under this protocol.
b:In France only.
c:As clinically indicated based on medical history, and/or signs/symptoms. Abnormal clinically significant findings must be reported as adverse events.
d:Conducted and read locally. Abnormal clinically significant observations must be reported as adverse events.

e:ECHO will be performed every 6 months, starting with Visit 1, unless more frequent ECHO is clinically indicated. Subjects in France will have repeat ECHO every 3 months.
f: In France and Netherlands only. Subjects enrolled in the Netherlands will have an additional chest x-ray 24 months after study completion and subjects enrolled in France will have additional chest x-rays 3 and 24 months after study completion.
g:As clinically indicated. A full physical and/or neurological examination may be performed, if warranted. Abnormal clinically significant observations must be reported as adverse events.
h:Females of child-bearing potential
i: For subjects who do not continue with commercially available ZX008, a follow-up will be performed 14 days after study completion or early termination and a follow-up ECHO, and physical examination will be performed 3 and 6 months after last dose. If any clinically significant observations are made on ECHO, a repeat ECHO will be performed every 3 months until resolved. Subjects enrolled in the United Kingdom will have an additional follow-up safety visit 12 months after the last dose; subjects enrolled in Germany and Netherlands will have an additional follow-up safety visit at 24 months after the last dose and subjects enrolled in France will have an additional follow-up safety visit at 3 and 24 months.
j: In Italy only.
k:Ongoing medications and ongoing adverse events should be captured in the CRF.
l: At the Principal Investigators discretion Study Drug can be collected/reviewed/dispensed at 3-month intervals.
m:Seizure Diary from core study to be reviewed, if applicable.
n:As appropriate based on last exam and reported AEs.

Country-specific Protocol Amendment 4.1 for the UK (22 September 2022)

Table 4: Schedule of Assessments for Subjects (UK only)

Study Assessments	OLE Treatment Period*				Follow-Up	Cardiac Follow-up
Visit Number	**Visit 1[a]**	**Telephone Visits 2, 4, 6, 8, 10, 12 (Months 3, 9, 15, 21, 27, 33)[b]**	**On-Site Visits 3, 5, 7, 9, 11 (Months 6, 12, 18, 24, 30)**	**Visit 13 (EOS/ET) Month 36**	**Visit 14 EOS/ET + 14 days**	**Visit 15/16[h] EOS/ET + 6 and 12 months**
Study Day	**1[a]**	**90, 270, 450, 630, 810, 990 (window: ±7 days)**	**180, 360, 540, 720, 900 (window: ±7 days)**	**1080 (window: ±7 days)**		**6 and 12 months post last dose**
Informed Consent	X[a]					
Entry Criteria Review	X					
Demographics	X					
Epilepsy History	X					
Abbreviated Physical/Neurological Examination	X[b]		X[g]	X	X[n]	X
Vital signs	X		X	X		
Weight, Height, BMI	X		X	X	X	
ECG [c,d]	X		X	X		X
Doppler ECHO[e]	X		X	X		X
Chest x-ray (France and Netherlands only)[c, f]	X		X	X		X
EEG (Italy only)[c, d, j]	X		X	X		
Pregnancy Test[h]	X		X	X		
Clinical laboratory evaluation (hematology/clinical chemistry)	X[c]		X[g]	X[g]		
Plasma sample for background AEDs			X[g]	X[g]		
C-SSRS	X		X	X		
Investigator CGI-Severity Rating (reference baseline)	X					
Parent/Caregiver CGI-Severity Rating (reference baseline)	X					
CGI-I (assessed by parent/caregiver)			X	X		
CGI-I (assessed by investigator)			X	X		
Overall change in seizure frequency (assessed by investigator)	X		X	X		

Study Assessments	OLE Treatment Period*				Follow-Up	Cardiac Follow-up
Visit Number	Visit 1[a]	Telephone Visits 2, 4, 6, 8, 10, 12 (Months 3, 9, 15, 21, 27, 33)[b]	On-Site Visits 3, 5, 7, 9, 11 (Months 6, 12, 18, 24, 30)	Visit 13 (EOS/ET) Month 36	Visit 14 EOS/ET + 14 days	Visit 15/16[h] EOS/ET + 6 and 12 months
Study Day	1[a]	90, 270, 450, 630, 810, 990 (window: ±7 days)	180, 360, 540, 720, 900 (window: ±7 days)	1080 (window: ±7 days)		6 and 12 months post last dose
Study Medication	D	C/R/D	C/R/D	C/R	C/R	
Seizure Diary	D	R (if applicable)[m]	R (if applicable)	R (if applicable)		
Concomitant Medications	X[k]	X	----------X----------			
Adverse Events	X[k]	X	----------X----------			

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

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

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

b:An unscheduled on-site visit (including safety assessments as per protocol) should be performed if considered necessary during the telephone visit, or at any other moment in-between the on-site visits, based on the investigator judgment.

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

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

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

f: In France and Netherlands only. Subjects in France and Netherlands will have an additional chest x-ray 24 months after study completion.

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

h:Females of child-bearing potential

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

j: In Italy only.

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

l: At the Principal Investigators discretion Study Drug can be collected/reviewed/dispensed at 3-month intervals.

m:Seizure Diary from core study to be reviewed, if applicable.

n:As appropriate based on last exam and reported AEs

Country-specific Protocol Amendment 3.1.1 for Denmark (20 November 2020)

Table 5: Schedule of Assessments for Subjects (Denmark only)

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

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

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

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

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

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

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

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

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

g: Females of child-bearing potential

h: A follow up will be performed 14 days after study completion or early termination and a follow-up ECHO, and physical examination will be performed 6 months after last dose. Subjects in the United Kingdom will have an additional follow-up 12 months after study completion; subjects in France, Germany, and Netherlands will have an additional follow-up 24 months after study completion.

i: In Italy only.

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

k: At the Principal Investigators discretion Study Drug can be collected/reviewed/dispensed at 3 month intervals.

l: Seizure Diary from core study to be reviewed, if applicable.

m: As appropriate based on last exam and reported AEs

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