Revisions to Version 1.0

New version /date: Version 2.0/09 Jul 2020

Change	Rationale	Affected Protocol Sections
Modified the exclusion criterion related to fenfluramine	Clarification	Section 2-Exclusion Criteria Section 9.3.2
Mentioned a statement that the randomization will be stratified by previous treatment with fenfluramine (yes/no)	Clarification	Section 2-Study design Section 2-Statistical Methods Section 9.1 Section 9.1.2 Section 9.7.1.6.1 Section 9.7.1.6.2 Section 9.7.1.6.3

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2023-A001-304
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of Lorcaserin as Adjunctive Treatment in Subjects with Dravet Syndrome
Sponsor:	Eisai Inc. 100 Tice Boulevard, Woodcliff Lake, New Jersey 07677 United States (US)
Sponsor's Investigational Product Name:	E2023/lorcaserin
Indication:	Dravet syndrome
Phase:	Phase 3
Approval Date:	Final (V1.0) 22 Jun 2020 (original protocol) V2.0 09 Jul 2020
IND Number:	148085
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2023

Name of Active Ingredient: lorcaserin

Study Protocol Title

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of Lorcaserin as Adjunctive Treatment in Subjects with Dravet Syndrome

Sites

Approximately 20 sites in the United States

Study Period and Phase of Development

Approximately 15 months

Phase 3

Objectives

Core Study

Primary Objective

- The primary objective of the study is to demonstrate that lorcaserin has superior efficacy compared to placebo on percent change in frequency of convulsive seizures per 28 days in subjects with Dravet syndrome.

Key Secondary Objective

- To evaluate whether lorcaserin has superior efficacy compared to placebo on the 50% responder rate (percent of subjects with at least 50% reduction in frequency of convulsive seizures per 28 days compared to baseline)

Other Secondary Objectives

- To evaluate whether lorcaserin has superior efficacy compared to placebo on the proportion of subjects who are free from convulsive seizures
- To characterize the pharmacokinetics (PK) of lorcaserin and the relationship between lorcaserin plasma concentrations, efficacy, and safety
- To evaluate the safety and tolerability of lorcaserin in subjects with Dravet syndrome

Exploratory Objectives

[redacted]

Extension Phase

Study Design

This is a multicenter, multiple-dose, randomized, double-blind, placebo-controlled, parallel-group adjunctive therapy study in subjects with Dravet syndrome. The study will consist of a Core Study and open-label Extension Phase.

Core Study

The Core Study will include a Prerandomization and a Randomization Phase.

The Prerandomization Phase will include a Screening/Baseline Period (4 weeks), during which the subjects will be assessed for eligibility.

Once the Screening and Baseline procedures have been completed and eligibility has been established, the subjects will be randomized and begin treatment in the Randomization Phase. Approximately 58 subjects will be randomized to 1 of 2 treatment groups in a ratio of 1:1 and will receive lorcaserin or placebo for 14 weeks. The randomization will be stratified by previous treatment with fenfluramine (yes/no) and by weight categories (10 to <20 kg, 20 to <40 kg, and ≥40 kg).

The Randomization Phase will consist of 2 periods: Treatment Period (14 weeks) and Follow-up Period (4 weeks).

During the Treatment Period, all subjects will take study drug twice daily (BID) based on weight according to the following table:

Subject's Weight	10 to <20 kg	20 to <40 kg	≥40 kg
Target Dose (starting)	2.5 mg BID (5 mg/day)	5 mg BID (10 mg/day)	10 mg BID (20 mg/day)
Dose Level Step (optional)	2.5 mg BID (5 mg/day)	5 mg BID (10 mg/day)	—
Maximum Dose	5 mg BID (10 mg/day)	10 mg BID (20 mg/day)	10 mg BID (20 mg/day)

BID = twice daily.

For lower weight categories, during the first 2 weeks of the Treatment Period, depending on the subject's clinical response and tolerability, the dose may be increased (not earlier than after 1 week of treatment) by 1 dose level at a visit. If the dose was increased, in the event of adverse events (AEs),

according to the investigator's clinical judgment, the dose may remain the same or can be decreased by 1 dose level, to the Target dose at any time during the Treatment Period. If the dose had been decreased, it may be increased again if tolerability improves.

All subjects who complete the Core Study will be eligible to enter the Extension Phase. The last visit of the Treatment Period of the Core Study is considered to be the 1st visit of the Extension Phase.

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for subjects who do not enter the Extension Phase.

Extension Phase

The Extension Phase will consist of a Treatment Period (12 weeks) and a Follow-up Period (4 weeks). Subjects are eligible to complete the Extension Phase only if they have completed the Treatment Period of the Core Study.

All subjects will receive lorcaserin during the entire Extension Phase but the dose level will be blinded during the first 6 weeks. During the first 6 weeks of the Extension Phase, subjects who received lorcaserin during the Core Study will receive the same dose of lorcaserin (the dose will remain flexible per weight category, based on clinical response and tolerability); subjects who received placebo during the Core Study will receive the target dose of lorcaserin per weight category. During the second 6 weeks of the Extension Phase, all subjects will receive lorcaserin at the maximum dose per weight category (the dose may be decreased due to tolerability reasons and increased again if tolerability improves). Addition, deletion, and dose changes to concomitant antiepileptic drugs (AEDs) are not allowed during the Treatment Period of the Extension Phase.

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for subjects who will not participate in the Extended Access Program (Study E2023-A001-405) after completion of this study. Subjects who complete the Extension Phase will be eligible to enter into Study E2023-A001-405.

Number of Subjects

Approximately 58 subjects will be randomized.

Inclusion Criteria

1. Male or female, age ≥2 years at the time of informed consent (or assent)
2. Confirmed diagnosis of epilepsy with Dravet syndrome per Recommendations from a North American Consensus Panel (2017)
3. Has had at least 4 convulsive seizures during the 4 weeks of the Prerandomization Phase
4. Currently treated with at least 1 AED and the doses of all AEDs must be stable for at least 4 weeks before Screening, and be expected to remain stable throughout the study.
5. If vagal nerve stimulator, responsive neurostimulator, or deep brain stimulator is used, it must be implanted at least 5 months before Screening, parameters must be stable for at least 4 weeks before Screening, and be expected to remain stable throughout the study
6. If a ketogenic diet is followed, it must be stable for at least 4 weeks before Screening and be expected to remain stable throughout the study

Exclusion Criteria

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
2. Females of childbearing potential who:

- Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
  - Total abstinence (if it is their preferred and usual lifestyle)
  - An intrauterine device or intrauterine hormone-releasing system
  - A contraceptive implant
  - An oral contraceptive (Subject must have been on a stable dose of the same oral contraceptive product for at least 28 days before dosing and must agree to stay on the same dose of the oral contraceptive throughout the study and for 28 days after study drug discontinuation).
  - Have a vasectomized partner with confirmed azoospermia

  Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

NOTE: All postmenarche females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

3. Use of lorcaserin within 4 weeks before Screening, or any history of it being discontinued due to lack of efficacy or adverse reactions
4. Use of fenfluramine within 2 months before Screening, any history of lack of fenfluramine efficacy, or any history of valvulopathy at baseline with history of fenfluramine use
5. Use of serotonergic or other prohibited drugs administered within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors within 30 days before dosing
6. Has a history of status epilepticus that required hospitalization during the 6 months before Screening
7. Currently has progressive central nervous system disease, other than Dravet syndrome, including degenerative central nervous system diseases and progressive tumors
8. Any history of malignancies
9. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal, liver disease) that in the opinion of the investigator could affect the subject's safety or interfere with the study assessments
10. Any history of or concomitant medical condition that in the opinion of the investigator would compromise the subject's ability to safely complete the study
11. A clinically significant electrocardiogram (ECG) abnormality, including a marked baseline prolonged QT/correct QT interval (eg, a repeated demonstration of a corrected QT interval >460 ms)
12. Any history of clinically significant bradycardia or other clinically significant conduction abnormality
13. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS] or based on investigator's clinical judgment for subjects unable to be evaluated by C-SSRS)
14. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS or based on investigator's clinical judgment for subjects unable to be evaluated by C-SSRS)

15. Hypersensitivity to the study drug and any of the excipients
16. Scheduled for surgery during the study
17. Use of illegal recreational drugs
18. Currently enrolled in another clinical study or used any investigational drug or device within 4 weeks before Screening or within approximately 5 half-lives, whichever is longer.

Study Treatments

Test drug: E2023, oral, 10-mg tablets

Comparator Drug: placebo, oral tablets matching the test drug

Study drug will be taken as a suspension BID approximately 12 hours apart.

To prepare the suspension of study drug before each administration, 2 tablets (from a blister pack, assigned by interactive voice and web response system [IxRS]) will first be suspended in 10 mL of water, after which 70 mL of sugar-free Ora-Sweet Syrup will be added and the suspension mixed thoroughly. For subjects with weight <20 kg, a 20 mL aliquot of this suspension, or for subjects with weight ≥20 kg, a 40 mL aliquot of this suspension will be taken orally and the remainder of the suspension should be discarded after each administration.

Duration of Treatment

14 weeks double-blind Treatment Period and 12 weeks open-label Extension Phase

Concomitant Drug/Therapy

Concomitant AEDs, including Epidiolex®, initiated before Screening are allowed; the dose must remain stable during the Prerandomization and Randomization Phase.

Benzodiazepines are allowed as AEDs or rescue medication for seizure control.

The following medications are prohibited during the Prerandomization and Randomization Phase: artisanal cannabidiol products, serotonergic drugs (due to the risk of serotonin syndrome), including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, triptans, bupropion, dextromethorphan, centrally-acting anorectic agents including fenfluramine, and St. John's Wort.

Drugs that are cytochrome P450 2D6 substrates should be used with caution, as lorcaserin can increase exposure of these drugs.

Investigational drugs or devices are prohibited during the participation in the study.

Assessments

Efficacy Assessments

Seizure diaries will be used to collect seizure counts.

CGIC (clinician-rated) will be assessed. CGIC is a 7-point scale that provides a clinician-determined summary measure of change from baseline of subject's clinical status.

Pharmacokinetic Assessments

Blood samples for PK assessment will be collected during the Treatment Period.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Data may be analyzed based on types of genetic mutations related to epilepsy (information on genetic mutation related to epilepsy will be collected, if available, based on review of epilepsy history).

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; regular laboratory evaluation for hematology, blood chemistry, and urinalysis; periodic measurement of vital signs, weight, echocardiograms, and ECGs; and the performance of physical and neurological examinations. An assessment of suicidality using the C-SSRS (for subjects aged ≥6 years old) or based upon clinical assessment of the investigator (for subjects <6 years old) will be performed at every study visit.

The C-SSRS provides assessment of suicide risk including the severity and immediacy of that risk through a series of plain-language questions.

Valvular regurgitation as assessed on echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, tricuspid, and pulmonic valve. The evaluations will be based on the recommendations from the American Society of Echocardiography. Pulmonary artery pressure will be estimated by a comprehensive approach that includes the tricuspid regurgitation jet velocity (if present), right ventricular outflow tract flow acceleration time, pulmonic regurgitation peak early diastolic velocity (if present), and the eccentricity index that describes the interventricular septum position at end-systole.

Other Assessments

Quality of life will be assessed using Quality of Life in Epilepsy Survey (QOLIE-31) and Pediatric Quality of Life Inventory (PedsQL 4.0).

The QOLIE-31 is a survey of health-related quality of life for adults that includes 31 questions about subject's health and daily activities.

The PedsQL 4.0 is a modular instrument for measuring health-related quality of life in children and adolescents ages 2 to 18 years old. Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL Disease-Specific Modules. The PedsQL 4.0 Generic Core Scales consist of 23 items applicable for healthy school and community populations, as well as pediatric populations with acute and chronic health conditions.

Bioanalytical Methods

Lorcaserin will be quantified in plasma using a validated liquid chromatography coupled with tandem mass spectrometry method.

Statistical Methods

<u>Core Study</u>

Primary Endpoint

- Percent change from baseline in seizure frequency of convulsive seizures per 28 days during the Treatment Period

Key Secondary Endpoint

- Proportion of 50% responders for convulsive seizures in the Treatment Period

Other Secondary Endpoints

- Proportion of subjects who are free from convulsive seizures in the Treatment Period
- PK parameters of lorcaserin in the Treatment Period
- Safety and tolerability, including incidence of treatment-emergent adverse events (TEAEs)

Exploratory Endpoints

[redacted]

[redacted]

Extension Phase

[redacted]

Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

The Full Analysis Set is the group of randomized subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement.

The PK Analysis Set is the group of all randomized subjects from whom at least measurable lorcaserin plasma concentration was obtained with associated documented dosing history.

Efficacy Analyses

Primary endpoint and other seizure types:

Seizure Frequency: Percent change from baseline in seizure frequency per 28 days for convulsive seizures, total seizures, non-convulsive and per seizure type during the Treatment Period of the Randomization Phase relative to the Prerandomization Phase will be analyzed using rank ANCOVA.

Seizure frequency will be based on number of seizures per 28 days, calculated during the Baseline Period and Treatment Period, as the number of seizures during each respective period divided by the number of non-missing days during each respective period, multiplied by 28. Analysis will be conducted using rank ANCOVA with treatment, fenfluramine and weight stratas, and site as factors, and the baseline seizure frequency as a covariate. In this analysis, all seizure frequency data will be rank transformed first for both baseline and endpoint seizure frequencies separately. The ANCOVA will be conducted based on the rank transformed data. Details will be specified in the statistical analysis plan.

Due to the expected skewed distribution of seizure frequency, median will be the primary statistics of interest for the primary endpoint, as well as for all other seizure frequency based continuous endpoints.

Sensitivity analysis: Multiple Imputation assuming missing not at random will be used to impute missing data for seizure frequency. Details will be specified in the statistical analysis plan.

Responder rate: An analysis of subjects who experience a 50% or greater reduction in convulsive seizure frequency in the Treatment Period of the Randomization Phase relative to the

Prerandomization Phase will be conducted based on Cochran-Mantel-Haenszel test adjusted for fenfluramine and weight stratas and site.

Sequential Gatekeeping Procedure

In order to control for Type I error, a sequential gatekeeping approach will be used where the primary endpoint will be tested first at 0.05 level, if the null hypothesis is rejected, the key secondary endpoint will be tested at 0.05 significance level. Otherwise no further testing will be performed.

Extension Phase: Descriptive statistics will be provided for the efficacy endpoints in the Extension Phase. Mean, standard deviation, median, minimum, and maximum will be provided for continuous endpoints and number and percentage will provide for categorical variables. In addition, plots will be used to summarize the data.

Pharmacokinetic Analyses

Analysis of PK will be performed on the PK Analysis Set. Plasma concentrations of lorcaserin will be listed.

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. For this approach, PK analysis data from this study will be pooled with relevant data from other lorcaserin studies as appropriate. The effect of covariates, such as baseline characteristics/demographics, on PK will be explored. Derived exposure parameters such as C_{max} and AUC at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships between exposure to lorcaserin and selected efficacy and safety endpoints will be explored graphically if data permit. Any emergent PK/pharmacodynamic relationship will be followed by population PK/pharmacodynamic modeling if data allow.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Data may be analyzed based on types of genetic mutations related to epilepsy.

Safety Analyses

Safety analyses will be conducted on the Safety Analysis Set. The data will be summarized by overall, treatment group, and by age group.

The incidence of TEAEs, serious adverse events (SAEs), AEs leading to discontinuation of study drug, and AEs leading to dose adjustment will be summarized. The incidence of TEAEs will be summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (related or not related). Proportion of subjects with increased seizure frequency, weight and body mass index changes will be summarized.

Changes from baseline in laboratory values will be summarized for continuous variables. Laboratory shift tables showing incidence of new or worsening clinically significant findings from baseline to the postbaseline visits will be displayed. Shift from baseline to the highest postbaseline laboratory value and from baseline to the lowest postbaseline laboratory value will also be displayed.

Incidence of treatment-emergent markedly abnormal laboratory values in laboratory safety test variables will be summarized. Treatment-emergent markedly abnormal laboratory values will be graded based on the Common Terminology Criteria for Adverse Events Version 5.0. Incidence of Hy's law will be summarized.

The change from baseline in vital signs and ECG parameters will be summarized.

Incidence of FDA-defined valvulopathy and pulmonary hypertension, and change from baseline of echocardiographic parameters will be summarized. Incidence of bradycardia, new onset heart block,

new onset of other arrhythmias or conduction abnormalities, thickened valve leaflets, and restricted valve leaflet motion will be summarized.

The duration of treatment will be calculated as the number of days between the date the subject receives their 1st treatment dose and the date the subject receives the last dose of treatment. These values will be used to summarize the extent of exposure to study drug.

Proportion of subjects with any treatment-emergent study-specific AEs will be summarized.

Other Analyses

The change from baseline in QOLIE-31 and PedsQL 4.0 Scale will be summarized.

Interim Analyses

No interim analysis is planned.

Sample Size Rationale

A sample size of 58 subjects (29 per group) will have 90% power to detect a difference of 50% reduction in convulsive seizure frequency per 28 days between lorcaserin and placebo assuming a standard deviation of 55, using a 2-group t-test with 0.05 two-sided significance level. This sample size will have 90% power to detect an odds-ratio of at least 10 for the secondary endpoint 50% reduction in convulsive seizure frequency, assuming the placebo response is 12%, using a 2-group Chi-square test with 0.05 two-sided significance level. This sample size assumes a 7% dropout rate.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
BID	twice daily
BMI	body mass index
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
5-HT	5-hydroxytryptamine
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IRB	Institutional Review Board
IxRS	interactive voice and web response system
MedDRA	Medical Dictionary for Regulatory Activities
PBPK	physiologically-based pharmacokinetic
PD	pharmacodynamics(s)
PedsQL 4.0	Pediatric Quality of Life Inventory
PK	pharmacokinetic(s)
POPPK	population pharmacokinetic
PT	preferred term
QOLIE-31	Quality of Life in Epilepsy Survey
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent and assent forms, and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)E6 (GCP), Section 3, and any local regulations (eg, Federal Regulations, Title 21 Code of Federal Regulations [CFR] Part 56). Any protocol amendment or revision to the informed consent and assent forms will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRAs], change of telephone number[s]). Documentation of IRB compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

Documented study approval from the IRB chairman must be sent to the principal investigator with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB to the sponsor.

Study progress is to be reported to IRB annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB of any reportable adverse events (AEs) per ICH guidelines and local IRB standards of practice. Upon completion of the study, the investigator will provide the IRB with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB within 90 days or sooner per the IRB requirements. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB within 15 calendar days or sooner as per the IRB requirements, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2013)

- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH
- Title 21 of the US 21 CFR regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent (or assent) document, the investigator must explain to each subject or guardian/legally authorized representative, in accordance with applicable professional standards and local laws/regulations, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject (or guardian/legally authorized representative), and the extent of maintaining confidentiality of the subject's records. Each subject (or guardian/legally authorized representative) must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the investigator.

This informed consent (or assent) should be given by means of a standard written statement, written in nontechnical language. Electronic media may be used to replace paper-based informed consent processes (electronic Informed Consent), utilizing electronic signatures. An electronic Informed Consent may be used to provide the same information that is contained within the written informed consent (or assent) document, evaluate the subject's comprehension of the information presented, and document the consent (or assent)of the subject or the subject's guardian/legally authorized representative. The subject or the subject's guardian/legally authorized representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a guardian/legally authorized representative is unable to read, an impartial witness should be present during the entire informed consent (or assent) discussion. After the informed consent form (ICF) (or assent form) and any other written information to be provided to subjects is read and explained to the subject or the subject's guardian/legally authorized representative, and after the subject or the subject's guardian/legally authorized representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject or subject's guardian/legally authorized representative will be asked to sign an ICF (or assent form) before any study-specific procedures are performed. No subject can enter the study before his/her informed consent (or assent) has been obtained. Informed consent from the subject's legally acceptable representative is always required and informed consent (or assent) from the subject is optional (when age and condition allows) if not required by local regulations. An informed consent will also be obtained from the guardian/legally authorized representative where applicable.

An unsigned copy of an IRB-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, Federal Regulations, Title 21 CFR Part 50). Each subject or guardian/legally authorized representative must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's guardian/legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 20 investigational sites in the US.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Compound Overview

Lorcaserin hydrochloride is a selective serotonin 5-hydroxytryptamine $(5\text{-HT})_{2C}$ receptor agonist that is being developed for treatment of Dravet syndrome. Lorcaserin hydrochloride selectively mimics the effects of 5-HT at the 5-HT_{2C} receptor and was designed to activate 5-HT_{2C} receptors without significant agonism of the 5-HT 2A (5-HT_{2A}) or 5-HT 2B (5-HT_{2B}) receptors at therapeutic doses. Functional assays indicate that lorcaserin selectivity for the human 5-HT_{2C} receptor is approximately 14- and 61-fold relative to the human 5-HT_{2A} and 5-HT_{2B} receptors, respectively, and showed little or no appreciable interaction with other 5-HT receptors, the 5-HT transporter, or a panel of additional receptors and ion channels.

Lorcaserin was approved by the US FDA on 27 Jun 2012 as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults.

During the review of a postmarketing required 12,000 patient cardiovascular outcome trial, the primary safety analysis showed no meaningful difference between lorcaserin and placebo in risk of major adverse cardiovascular events, demonstrating noninferiority (Bohula et al., 2018). An assessment of malignancies in this study showed a small numerical imbalance (0.6%) in the lorcaserin arm with 462 (7.7%) lorcaserin-treated subjects diagnosed with 520 primary cancers and 423 (7.1%) placebo-treated subjects diagnosed with 470 cancers (based on an FDA analysis). While the data did not support a finding of causation with respect to such cancers, the FDA determined that this numerical imbalance in malignancies nonetheless resulted in an unfavourable benefit:risk for the weight management

indication and on 11 Feb 2020, the FDA requested that Eisai voluntarily withdraw BELVIQ® from the market.

After the public announcement of the BELVIQ withdrawal, direct requests were made to Eisai and FDA by physicians, caregivers, and advocacy groups regarding the future availability of lorcaserin for the treatment of refractory epilepsies, such as Dravet syndrome. After consultation with the FDA, Eisai has made lorcaserin available via an Extended Access Program for refractory epilepsies to patients who were prescribed BELVIQ before the market withdrawal announcement and, based on their treating physician judgment, continue to derive clinical benefit.

For more details refer to the Global Investigator Brochure.

7.2 Clinical Experience

Tolete et. al (2018) summarize a retrospective chart review (Jan 2014 – Jan 2018) of 36 patients with childhood-onset refractory epilepsies (Dravet syndrome [20 patients], Lennox-Gastaut syndrome [9 patients], other treatment-resistant focal epilepsies [3 patients], and generalized epilepsies [3 patients]) administered lorcaserin. Thirty-three (94.3%) patients were taking at least 1 antiseizure medication (mean = 3; clobazam [60%], valproic acid [57.1%], and cannabidiol [40%]). Of the 35 patients analyzed, the median percentage reduction from baseline in the mean monthly frequency of motor seizures was 47.7% ($z=-3.04$, $P<0.01$; 46.9% in tonic-clonic, 62.3% in tonic, 60.1% in atonic, and 54.6% in focal seizures with motor features); 15 (42%) had greater than 50% reduction in motor seizures. Two (5.7%) patients had increased seizure frequency. The mean lorcaserin dosage was 15.7 mg/d (and 13.7 mg/d for children) and median treatment duration was 10.8 months. After 15 months, 50% of patients remained on lorcaserin. The most common AEs reported were decreased appetite (19.6%), decreased attentiveness (17.1%), and weight loss (11.1%). The mean decline in body mass index (BMI) at last follow-up compared to baseline was -0.58 ± 0.24 kg/m^2 (-2.7 ± 1.3%; $P=0.02$) and was similar among patients taking or not taking valproate. Five patients stopped treatment before 30 days due to side effects. The above nonclinical and clinical information on lorcaserin justifies the development of lorcaserin in Dravet.

The study design and duration of treatment was selected based on Guidelines for Industry on Clinical Evaluation of Antiepileptic Drugs (FDA, 1997) and is similar to the design of registration clinical studies of Epidiolex, drug approved for treatment of Dravet syndrome (Devinsky et al., 2017) and recently reported fenfluramine study in Dravet syndrome (Lagae et al., 2020). Sample size was estimated based on the percent reduction of convulsive seizures and standard deviation reported in fenfluramine study in Dravet syndrome (Lagae et al., 2020).

7.3 Study Rationale

Dravet syndrome is a severe refractory epilepsy syndrome with a reported incidence of 1 in 40,000 (Wu et al., 2015), onset in the first year of life, and is characterized by frequent

convulsive seizures that may contribute to intellectual disability and impairments in coordination, behavior, and cognition (Dravet, 1978). Most patients (70% to 85%) have mutation in the sodium voltage-gated channel alpha subunit 1 (SCN1A) gene. The diagnosis of Dravet syndrome is based on electroclinical criteria (Wirrell et al., 2017).

Lorcaserin hydrochloride is a selective serotonin 5-HT_{2C} receptor agonist. The 5-HT_{2C} receptor is found primarily in the central nervous system (CNS). Autoradiographic studies in rats and other species have demonstrated that 5-HT_{2C} binding sites are widely distributed in regions fundamental to the generation and propagation of seizures, including in the cortex (olfactory nucleus, pyriform, cingulate, and retrosplenial), limbic system (nucleus accumbens, hippocampus, and amygdala), and the basal ganglia (caudate nucleus and substantia nigra) (Isaac, 2005). At the cellular level, 5-HT_{2C} receptors are expressed on a subpopulation of inhibitory interneurons, and activation of these receptors increases gamma aminobutyric acid-mediated synaptic inhibition (Boothman et al., 2006). As decreased inhibition plays a key role in the generation of seizures in Dravet syndrome, there is strong physiologic rationale for the therapeutic use of a selective 5-HT_{2C} agonist, such as lorcaserin, in Dravet syndrome. Fenfluramine, an agonist at the 5-HT_{2B} and 5-HT_{2C} receptors, has demonstrated efficacy in Dravet syndrome, further supporting the therapeutic rationale for lorcaserin (Lagae et al., 2020).

Mice lacking 5-HT_{2C} receptors, the target for lorcaserin, display spontaneous seizures that are occasionally lethal, and a decreased threshold for various convulsing stimuli (Venzi et al., 2016). It has been demonstrated that the scn1labs552 zebrafish models the sodium channel mutation, convulsions, electrographic changes, and pharmacological responses to treatment of Dravet syndrome (Griffin, et al., 2018), and lorcaserin has been shown to reduce seizures in this zebrafish Dravet syndrome model (Griffin et al., 2017; Griffin et al., 2018). These nonclinical and clinical data support development of lorcaserin as an antiseizure agent for treatment of Dravet syndrome.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to demonstrate that lorcaserin has superior efficacy compared to placebo on percent change in frequency of convulsive seizures per 28 days in subjects with Dravet syndrome.

8.2 Secondary Objectives

8.2.1 Key Secondary Objective

- The key secondary objective of the study is to evaluate whether lorcaserin has superior efficacy compared to placebo on the 50% responder rate (percent of subjects with at least 50% reduction in frequency of convulsive seizures per 28 days compared to baseline).

8.2.2 Other Secondary Objectives

- To evaluate whether lorcaserin has superior efficacy compared to placebo on the proportion of subjects who are free from convulsive seizures
- To characterize the pharmacokinetics (PK) of lorcaserin and the relationship between lorcaserin plasma concentrations, efficacy, and safety
- To evaluate the safety and tolerability of lorcaserin in subjects with Dravet syndrome

8.3 Exploratory Objectives

CCI

[redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, multiple-dose, randomized, double-blind, placebo-controlled, parallel-group adjunctive therapy study in subjects with Dravet syndrome. The study will consist of a Core Study and open-label Extension Phase.

The Core Study will include a Prerandomization and a Randomization Phase.

The Prerandomization Phase will include a Screening/Baseline Period (4 weeks), during which the subjects will be assessed for eligibility.

Once the Screening and Baseline procedures have been completed and eligibility has been established, the subjects will be randomized and begin treatment in the Randomization Phase. Approximately 58 subjects will be randomized to 1 of 2 treatment groups in a ratio of 1:1 and will receive lorcaserin or placebo for 14 weeks. The randomization will be stratified by previous treatment with fenfluramine (yes/no) and by weight categories (10 to <20 kg, 20 to <40 kg, and ≥40 kg).

The Randomization Phase will consist of 2 periods: Treatment Period (14 weeks) and Follow-up Period (4 weeks).

During the Treatment Period, all subjects will take study drug twice daily (BID) based on weight as described in Section 9.4.1.

For lower weight categories, during the first 2 weeks of Treatment Period, depending on the subject's clinical response and tolerability, the dose may be increased (not earlier than after 1 week of treatment) by 1 dose level at a visit. If the dose was increased, in the event of AEs, according to the investigator's clinical judgment, the dose may remain the same or can be decreased by 1 dose level, to the Target dose at any time during the Treatment Period. If the dose had been decreased, it may be increased again if tolerability improves.

All subjects who complete the Core Study will be eligible to enter the Extension Phase (refer to Appendix 2). The last visit of the Treatment Period of the Core Study is considered to be the 1st visit of the Extension Phase.

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for subjects who do not enter the Extension Phase.

An overview of the study design is presented in Figure 1.

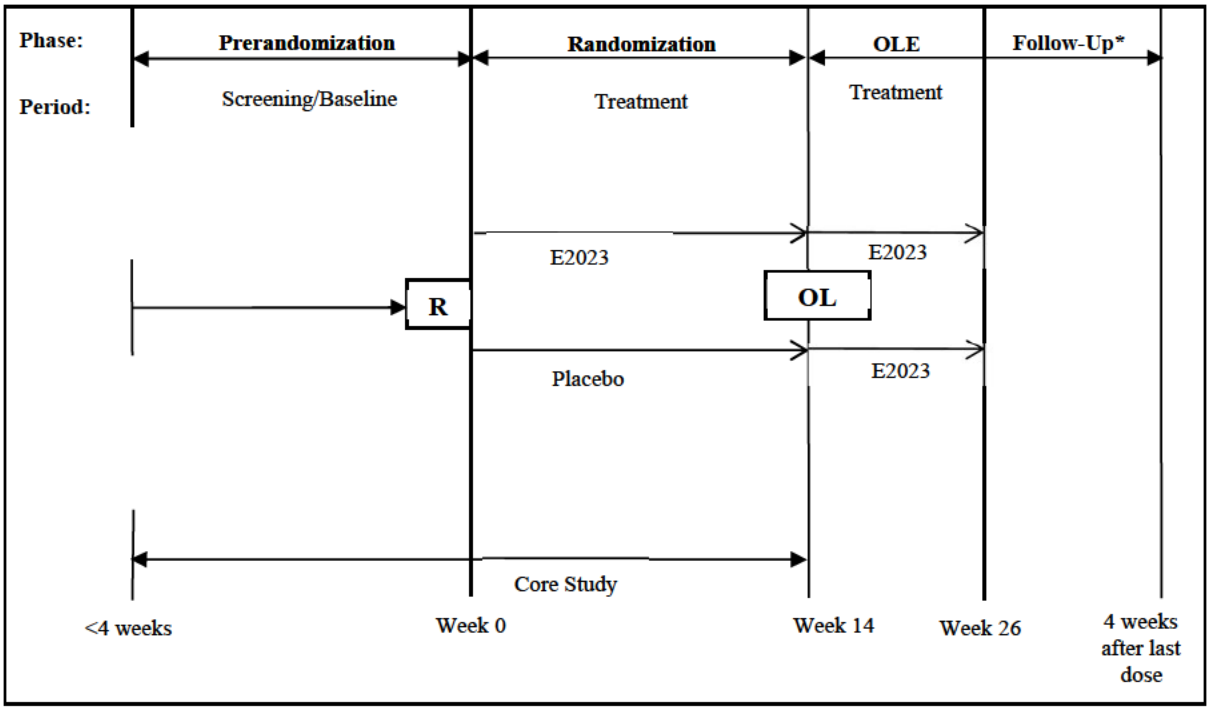

Figure 1 Study Design: E2023-A001-304 Core Study and Extension Phase

Follow-up can occur during the Randomization Phase (if the subject discontinued during the Randomization Phase), or during the Extension Phase, after the termination of study treatment.

*All subjects will have follow-up 4 weeks after the end of the treatment and a final assessment completed.

OL = open-label, OLE = open-label extension, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase will last for 4 weeks and will include a Screening/Baseline Period, during which the subjects will be assessed for eligibility.

9.1.1.1 Screening/Baseline Period

The Screening/Baseline Period will begin at Visit 1 (from Week –4 to Week 0). The purpose of the Screening Period is to obtain informed consent and assent forms and to establish protocol eligibility. Informed consent (or assent) will be obtained after the study has been fully explained to each subject and/or guardian/legally authorized representative and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent (or assent) are detailed in Section 5.3.

Subjects must have a diagnosis of epilepsy with Dravet syndrome according to Recommendations from a North American Consensus Panel (2017) and confirmed by past EEG and clinical history.

During the 4-week Baseline Period, subjects must have at least 4 convulsive seizures based on seizure diary. Convulsive seizures are defined as hemiclonic, tonic, clonic, tonic-atonic, generalized tonic-clonic, and focal with clearly observable motor signs.

All concomitant treatment for epilepsy (including doses of antiepileptic drugs [AEDs], parameters of vagal nerve stimulator, responsive neurostimulator, or deep brain stimulator, and ketogenic diet, if followed) must be stable for at least 4 weeks before Screening and remain stable throughout the Core Study.

Once the Screening and Baseline procedures have been completed and eligibility has been established (Sections 9.3.1 and 9.3.2), the subjects will be randomized and begin treatment in the Randomization Phase.

9.1.2 Randomization Phase

The duration of the Randomization Phase will be 14 weeks and will include 2 periods: Treatment and Follow-up. Subjects whose screening assessments and evaluations are completed and reviewed by the principal investigator and who continue to meet all of the inclusion/exclusion criteria will enter the Randomization Phase. Approximately 58 subjects will be randomized to 1 of 2 treatment groups in a ratio of 1:1 and will receive lorcaserin or placebo for 14 weeks. The randomization will be stratified by previous treatment with fenfluramine (yes/no) and by weight categories (10 to <20 kg, 20 to <40 kg, and ≥40 kg).

9.1.2.1 Treatment Period

During the Treatment Period, all subjects will take study drug BID based on weight according to Section 9.4.1.

For lower weight categories, during the first 2 weeks of the Treatment Period, depending on the subject's clinical response and tolerability, the dose may be increased (not earlier than after 1 week of treatment) by one dose level at a visit. If the dose was increased, in the event of AEs, according to the investigator's clinical judgment, the dose may remain the same or can be decreased by 1 dose level, to the target dose at any time during the Treatment Period. If the dose had been decreased, it may be increased again if tolerability improves.

All subjects who complete the Core Study will be eligible to enter the Extension Phase. The last visit of the Treatment Period of the Core Study is considered to be the 1st visit of the Extension Phase.

9.1.2.2 Follow-Up Period

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for subjects who do not enter the Extension Phase.

9.1.3 Extension Phase

The Extension Phase will consist of a Treatment Period (12 weeks) and a Follow-up Period (4 weeks). Subjects are eligible to complete the Extension Phase only if they have completed the Treatment Period of the Core Study.

All subjects will receive lorcaserin during the entire Extension Phase but the dose level will be blinded during the first 6 weeks. During the first 6 weeks of the Extension Phase, subjects who received lorcaserin during the Core Study will receive the same dose of lorcaserin (the dose will remain flexible per weight category, based on clinical response and tolerability); subjects who received placebo during the Core Study will receive the target dose of lorcaserin per weight category. During the second 6 weeks of the Extension Phase, all subjects will receive lorcaserin at the maximum dose per weight category (the dose may be decreased due to tolerability reasons and increased again if tolerability improves). Addition, deletion, and dose changes to concomitant AEDs are not allowed during the Treatment Period of the Extension Phase.

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for subjects who will not participate in the Extended Access Program (Study E2023-A001-405) after completion of this study. Subjects who complete the Extension Phase will be eligible to enter into Study E2023-A001-405. See Appendix 2 for a full description of the Extension Phase.

9.2 Discussion of Study Design, Including Choice of Control Groups

The study design and duration of treatment was selected based on Guidelines for Industry on Clinical Evaluation of Antiepileptic Drugs (FDA, 1997) and is similar to the design of registration clinical studies of Epidiolex, a drug approved for treatment of Dravet syndrome (Devinsky et al., 2017) and a recently reported fenfluramine study in Dravet syndrome (Lagae et al., 2020). Sample size was estimated based on the percent reduction of convulsive seizures and standard deviation reported in the fenfluramine study in Dravet syndrome (Lagae et al., 2020).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

9.3 Selection of Study Population

Approximately 58 subjects will be randomized at approximately 20 sites in the US. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Male or female, age ≥2 years at the time of informed consent (or assent)
2. Confirmed diagnosis of epilepsy with Dravet syndrome per Recommendations from a North American Consensus Panel (2017)
3. Has had at least 4 convulsive seizures during the 4 weeks of the Prerandomization Phase
4. Currently treated with at least 1 AED and the doses of all AEDs must be stable for at least 4 weeks before Screening, and be expected to remain stable throughout the study.
5. If vagal nerve stimulator, responsive neurostimulator, or deep brain stimulator is used, it must be implanted at least 5 months before Screening, parameters must be stable for at least 4 weeks before Screening, and be expected to remain stable throughout the study
6. If a ketogenic diet is followed, it must be stable for at least 4 weeks before Screening and be expected to remain stable throughout the study

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
2. Females of childbearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - Total abstinence (if it is their preferred and usual lifestyle)
     - An intrauterine device or intrauterine hormone-releasing system
     - A contraceptive implant
     - An oral contraceptive (Subject must have been on a stable dose of the same oral contraceptive product for at least 28 days before dosing and must agree to stay on the same dose of the oral contraceptive throughout the study and for 28 days after study drug discontinuation).
     - Have a vasectomized partner with confirmed azoospermia
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   NOTE: All postmenarche females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).
3. Use of lorcaserin within 4 weeks before Screening, or any history of it being discontinued due to lack of efficacy or adverse reactions
4. Use of fenfluramine within 2 months before Screening, any history of lack of fenfluramine efficacy, or any history of valvulopathy at baseline with history of fenfluramine use
5. Use of serotonergic or other prohibited drugs administered within 7 days (or 5 half-lives, whichever is longer) or monoamine oxidase inhibitors within 30 days before dosing
6. Has a history of status epilepticus that required hospitalization during the 6 months before Screening
7. Currently has progressive CNS disease, other than Dravet syndrome, including degenerative CNS diseases and progressive tumors
8. Any history of malignancies
9. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal, liver disease) that in the opinion of the investigator could affect the subject's safety or interfere with the study assessments
10. Any history of or concomitant medical condition that in the opinion of the investigator would compromise the subject's ability to safely complete the study

11. A clinically significant electrocardiogram (ECG) abnormality, including a marked baseline prolonged QT/corrected QT interval (QTc; eg, a repeated demonstration of a QTc >460 ms)
12. Any history of clinically significant bradycardia or other clinically significant conduction abnormality
13. Any suicidal ideation with intent with or without a plan at Screening or within 6 months of Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale [C-SSRS] or based on investigator's clinical judgment for subjects unable to be evaluated by C-SSRS)
14. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS or based on investigator's clinical judgment for subjects unable to be evaluated by C-SSRS)
15. Hypersensitivity to the study drug and any of the excipients
16. Scheduled for surgery during the study
17. Use of illegal recreational drugs
18. Currently enrolled in another clinical study or used any investigational drug or device within 4 weeks before Screening or within approximately 5 half-lives, whichever is longer.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Follow-Up Period and complete protocol-specified off-treatment visits and procedures. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, or whether the subject will withdraw from the study. If a subject or guardian/legally authorized representative withdraws consent (or assent), the date will be documented in the source documents.

A subject who discontinues study treatment should be followed for subsequent protocol-specified visits and procedures. If a subject discontinues study drug but remains in the study, the set of end-of-treatment procedures, Early Treatment Discontinuation according to Early Discontinuation Visit schedule, will be administered, and further information will be collected at visits according to regular Schedule of Procedures/Assessments. The primary reason for discontinuation and all other reasons contributing to the subject's discontinuation from study drug will be collected. If a subject discontinues from study treatment and the study at the same time, Early Discontinuation Visit will be conducted followed by safety Follow-up Visit (see Section 9.5.5).

9.4 Treatments

9.4.1 Treatments Administered

The following study drugs will be used in this study:

- Test drug: E2023, oral, 10-mg tablets
- Comparator drug: placebo, oral tablets matching the test drug

Selection of dose, timing, and instruction on how to prepare suspension for individual subjects is described in Section 9.4.5.

9.4.2 Identity of Investigational Products

Lorcaserin and matching placebo will be provided as a blue-colored, film-coated, 10-mg tablet, round, biconvex, debossed "A" on one side and "10" on the other side.

Investigational products, ie, lorcaserin and placebo, will be supplied by the sponsor in blinded labeled containers.

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study drug will consist of either lorcaserin or placebo.

9.4.2.1 Chemical Name of E2023

- Test drug code: E2023
- Generic name: Lorcaserin
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{14}ClN \cdot HCl \cdot 0.5\ H_2O$
- Molecular weight: 241.16 g/mol

9.4.2.2 Comparator Drug

The comparator drug is placebo, oral tablets matching the test drug.

9.4.2.3 Labeling for Study Drug

Lorcaserin or matching placebo will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After the Baseline Period, subjects will be randomized to 1 of 2 treatment groups in a ratio of 1:1. Each treatment group will receive either lorcaserin or placebo BID.

Randomization will be performed centrally by an interactive voice and web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (and after successful completion of Visit 1), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique 6-digit randomization number. At every subsequent dose change, the investigator or a designee will call the IxRS to obtain dispensing instructions and register the subject's visit.

9.4.4 Selection of Doses in the Study

Population pharmacokinetic (POPPK) modeling of lorcaserin in a pooled population of healthy adult volunteers from 2 Phase 1 studies, and overweight and obese adults from 1 Phase 2 study and 3 Phase 3 studies (Report CMPS-APD356-003R), has identified that the PK profile of lorcaserin is best described by a 1-compartment model with first order absorption and elimination. The analysis also identified that exposures to lorcaserin are a function of body weight, with allometric body weight effects on both clearance (exponent=0.75) and volume of distribution (exponent=1).

In addition, a physiologically-based pharmacokinetic (PBPK) model was developed for lorcaserin using Simcyp V19. Performance of the model in predicting lorcaserin PK was verified by plotting the model-predicted PK profiles over the observed lorcaserin PK profiles in healthy volunteers from Studies APD356-001 (single ascending dose), APD356-002 (multiple ascending dose) and APD356-101 (immediate-release vs extended-release bioequivalence study). Overall, the model predicted the PK profiles of lorcaserin well and was considered suitable for predicting lorcaserin PK profiles in children.

Both the POPPK model and the PBPK model were used to simulate lorcaserin PK profiles for a range of doses and body weights in children (Centers for Disease Control and Prevention, 2020). The lower limit of the body weight for Group 1 (10 kg), represents the 10th percentile of body weight distribution in a 2 year-old child, according to the Centers for Disease Control and Prevention. PBPK simulations of lorcaserin PK profiles were performed using the default values of the Simcyp Pediatric population file. Both methods predicted similar PK profiles for lorcaserin in the age range evaluated (2 to 7 years).

The doses of lorcaserin proposed for this study were selected based on the similarities of the predicted PK profile with those predicted after lorcaserin 10 mg BID administration in a 70 kg adult.

The doses proposed are further supported by data from a Good Laboratory Practice repeated-dose toxicity study in juvenile Sprague Dawley rats at doses of 0, 5, 50, and 100 mg/kg/day. Juvenile and adult Sprague Dawley rats tolerate lorcaserin at similar doses and exposures and the toxicity profile of lorcaserin is similar between juvenile and adult rats. Significant findings noted in the juvenile toxicity study were delayed sexual maturity in females and increased incidence and extent of tubuloalveolar glandular tissue of mammary gland in males compatible with increased prolactin levels at the highest dose tested (100 mg/kg/day). These findings were absent at the mid-dose (50 mg/kg/day) providing 15- and 10-fold exposure margins in females and males, respectively, relative to the highest anticipated mean daily exposure in the proposed clinical study (10 mg BID for a 40 kg child).

9.4.5 Selection and Timing of Dose for Each Subject

During the Treatment Period, all subjects will take study drug as a suspension BID approximately 12 hours apart based on weight according to Table 1.

Table 1 Selection of Dose

Subject's Weight	10 to <20 kg	20 to <40 kg	≥40 kg
Target Dose(starting)	2.5 mg BID (5 mg/day)	5 mg BID (10 mg/day)	10 mg BID (20 mg/day)
Dose Level Step (optional)	2.5 mg BID (5 mg/day)	5 mg BID (10 mg/day)	—
Maximum Dose	5 mg BID (10 mg/day)	10 mg BID (20 mg/day)	10 mg BID (20 mg/day)

BID = twice daily.

To prepare the suspension of study drug before each administration, 2 tablets (from a blister pack, assigned by IxRS) will first be suspended in 10 mL of water, after which 70 mL of sugar-free Ora-Sweet Syrup will be added and the suspension mixed thoroughly. For subjects with weight <20 kg, a 20 mL aliquot of this suspension, or for subjects with weight ≥20 kg, a 40 mL aliquot of this suspension will be taken orally and the remainder of the suspension should be discarded after each administration (for details see Appendix 3).

9.4.6 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per SOP.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study starting at the date of informed consent (or assent) will be recorded. The AE or medical condition for which the concomitant medication or therapy was administered will be recorded.

Concomitant AEDs, including Epidiolex®, initiated before Screening are allowed; the dose must remain stable during the Prerandomization and Randomization Phase.

Benzodiazepines are allowed as AEDs or rescue medication for seizure control.

The following medications are prohibited during the Prerandomization and Randomization Phase: Artisanal cannabidiol products, serotonergic drugs (due to the risk of serotonin syndrome), including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, triptans, bupropion, dextromethorphan, centrally-acting anorectic agents including fenfluramine, and St. John's Wort.

Drugs that are cytochrome P450 2D6 substrates should be used with caution, as lorcaserin can increase exposure of these drugs.

Investigational drugs or devices are prohibited during the participation in the study.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. CRAs will review treatment compliance during visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- Drug Enforcement Agency license
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB for the institution where the study is to be conducted
- A copy of the IRB-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Form FDA 1572
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical site agreement

The investigator and the study staff will be responsible for the accountability of all treatment (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the treatment to be used other than as directed by this protocol. Parent/guardian may be dispensed treatment for pediatric subjects.

The site must maintain an accurate and timely record of the following: receipt of all study treatment, dispensing of treatment to the subject, collection and reconciliation of unused study treatment of reconciled study treatment to the sponsor or (where applicable) destruction of reconciled study treatment at the site. This includes, but may not be limited to: (a) documentation of receipt of study treatment, (b) treatment dispensing/return reconciliation

log, (c) treatment accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of treatment that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The treatment and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority. As applicable, all unused treatment and empty and partially empty containers from used study treatment are to be returned to the investigator by the subject and, together with unused study treatment that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of treatment and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of treatment to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, treatment that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, treatment may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where treatment is approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

Assessments will be performed as specified in Table 3.

9.5.1.1 Screening Assessments

9.5.1.1.1 DEMOGRAPHY

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth, sex, race/ethnicity.

Height and weight will be measured at the Screening Visit.

9.5.1.1.2 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 1 year must be noted in the Medical History and Current Medical Conditions case report form (CRF).

9.5.1.1.3 EPILEPSY HISTORY

Epilepsy history will be will be recorded at Screening Visit as designated in the Schedule of Procedures/Assessments (Table 3). Epilepsy history will include information on genetic mutation related to epilepsy, if available.

9.5.1.2 Efficacy Assessments

9.5.1.2.1 SEIZURE COUNTS

Seizure diaries will be used to collect seizure counts. Diaries will be dispensed to all subjects at each visit as described in Table 3. The diary is to be completed daily, by the parent/guardian. All seizures will be recorded. At each visit the parent/guardian will be instructed by the site personnel as to how to complete the diary and reminded that they must return the diary at their next scheduled clinic visit and at the Early Discontinuation and Follow-up Visits (if applicable). To ensure correct seizure classification, the medically qualified investigator should review the diary with the parent/guardian at all visits. Parents/guardians must be counseled if diary compliance is not satisfactory (ie, missed 3 or more consecutive daily diary entries).

9.5.1.2.2 CLINICAL GLOBAL IMPRESSION

CGIC (clinician-rated) will be assessed. CGIC is a 7-point scale that provides a clinician-determined summary measure of change from baseline of subject's clinical status.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Blood samples for PK assessment will be collected during the Treatment Period.

Blood samples with sodium heparin as anticoagulant (1 mL each) will be collected as specified in Table 3. See PK or laboratory manual for a description of collection, handling, and shipping procedures for PK samples.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of lorcaserin will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood will also be drawn where possible at the first report of a serious adverse event (SAE) or severe unexpected AE and at its resolution.

9.5.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Data may be analyzed based on types of genetic mutations related to epilepsy (information on genetic mutation related to epilepsy will be collected, if available, based on review of epilepsy history).

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, regular laboratory evaluation for hematology, blood chemistry, and urinalysis; periodic measurement of vital signs, weight, echocardiograms, and ECGs; and the performance of physical and neurological examinations, as detailed in Table 3.

An assessment of suicidality using the C-SSRS (for subjects aged ≥6 years old) or based upon clinical assessment of the investigator (for subjects <6 years old) will be performed at every study visit. The C-SSRS provides assessment of suicide risk including the severity and immediacy of that risk through a series of plain-language questions.

Valvular regurgitation as assessed on echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, tricuspid, and pulmonic valve. The evaluations will be based on the recommendations from the American Society of Echocardiography (Zoghbi et al., 2017). Pulmonary artery pressure will be estimated by a comprehensive approach that includes the tricuspid regurgitation jet velocity (if present), right ventricular outflow tract flow acceleration time, pulmonic regurgitation peak early diastolic velocity (if present), right ventricular outflow tract flow acceleration time, pulmonic regurgitation peak early diastolic velocity (if present), and the eccentricity index that describes the interventricular septum position at end-systole (Jone and Ivy, 2014).

9.5.1.4.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2023 or placebo.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug

- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit of the End of Treatment Phase. Refer to Section 9.5.4.1 for the time period after the end of treatment for SAE collection.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTc using Fridericia's formula) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc using Fridericia's formula is more than 460 ms and there is an increase of more than 60 ms from baseline. If subject has a normal ECG baseline reading, but during any visit thereafter the QT is measured as more than 460 ms, 3 consecutive ECGs separated by 5 to 10 minutes will be performed to confirm the abnormality. Any ECG abnormality that the investigator considers as an AE should be reported as such.

It is the responsibility of the investigator to review the results of the clinical assessment of suicidality, C-SSRS, in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE.

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.4.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility

9.5.1.4.2 Serious Adverse Events and Events Associated with Special Situations

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

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Refer to Section 9.5.1.4.3 for the list of study-specific events to be reported as SAEs.

In addition to study-specific events, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (or assent) (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.4.3 Study-Specific Adverse Events

The following study-specific AEs will be considered as always serious as an important medical event, in the absence of other seriousness criteria: serotonin syndrome, psychosis, suicidal behavior, priapism, new or worsened valvular heart disease, new or worsened pulmonary hypertension, new arrhythmia or conduction abnormality, severe symptomatic hypoglycemia, and malignant neoplasms. The definitions of these study-specific AEs and the instructions for reporting are described in Section 9.5.4.3.3.

9.5.1.4.4 Laboratory Measurements

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 2. Subjects should be in a seated position during blood collection.

The Schedule of Procedures/Assessments (Table 3) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 2 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Calcium, chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

RBC = red blood cell, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the CRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF (see Section 9.5.4.3.2).

9.5.1.4.5 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade], and weight [kg]) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 3) by a validated method. Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. All blood pressure measurements should be performed on the same arm, preferably by the same person.

9.5.1.4.6 Physical Examinations

Physical examinations (comprehensive or symptom directed) will be performed as designated in the Schedule of Procedures/Assessments (Table 3). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest

(including heart and lungs), abdomen, limbs, and skin. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.4.7 NEUROLOGICAL EXAMINATION

Neurological examination will consist of assessment of mental status, sensory systems, cranial nerves, motor function, deep tendon reflexes, and cerebellar functions.

9.5.1.4.8 ELECTROCARDIOGRAMS

ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 3). If subject has a normal ECG baseline reading, but during any visit thereafter the QT is measured as more than 460 ms, 3 consecutive ECGs separated by 5 to 10 minutes will be performed to confirm the abnormality.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.4.9 ECHOCARDIOGRAMS

Echocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 3).

In this study, echocardiographic images will be acquired as part of safety assessments. Standardized training will be provided for all echocardiographers, and centralized procedures for collecting, analyzing, and reporting echocardiographic data will be implemented. All echocardiograms will be over-read by 2 blinded central readers (primary and secondary). The baseline echocardiograms will be performed before randomization between Visits 1 and 2 for subjects who are considered otherwise eligible for the study based on initial review of eligibility criteria. Valvular regurgitation as assessed on echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, tricuspid, and pulmonic valves. The evaluations will be based on the recommendations from the American Society of Echocardiography (Zoghbi et al., 2017). Pulmonary artery pressure will be estimated by a comprehensive approach that includes the tricuspid regurgitation jet velocity (if present), right ventricular outflow tract flow acceleration time, pulmonic regurgitation peak early diastolic velocity (if present), right ventricular outflow tract flow acceleration time, pulmonic regurgitation peak early diastolic velocity (if present), and the eccentricity index that describes the interventricular septum position at end-systole (Jone and Ivy, 2014).

9.5.1.4.10 OTHER SAFETY ASSESSMENTS

C-SSRS

An assessment of suicidality using the C-SSRS will be performed at Screening, Baseline, Day 1 postdosing, every visit, including after the last dose of study drug, and at the Termination Visit, as designated in the Schedule of Procedures/Assessments (Table 3).

Pregnancy Test

A serum β-hCG test will be performed for female subjects age 12 years old and above, or of child-bearing potential, only. A sample of blood will be taken at Screening; at all other time points a urine pregnancy test will be performed as specified in the Schedule of Procedures/Assessments (Table 3). If urine cannot be obtained for pregnancy testing after Screening, a serum pregnancy test will be performed.

9.5.1.5 Other Assessments

9.5.1.5.1 QUALITY OF LIFE IN EPILEPSY SURVEY

Quality of life will be assessed using Quality of Life in Epilepsy Survey (QOLIE-31). The QOLIE-31 is a survey of health-related quality of life for adults that includes 31 questions about subject's health and daily activities.

9.5.1.5.2 PEDIATRIC QUALITY OF LIFE INVENTORY

The Pediatric Quality of Life Inventory (PedsQL 4.0) is a modular instrument for measuring health-related quality of life in children and adolescents ages 2 to 18 years. Generic Core Scales are multidimensional child self-report and parent proxy-report scales developed as the generic core measure to be integrated with the PedsQL Disease-Specific Modules. The PedsQL 4.0 Generic Core Scales consist of 23 items applicable for healthy school and community populations, as well as pediatric populations with acute and chronic health conditions.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the Schedule of Procedures/Assessments for the Core Study.

Table 3 Schedule of Procedures/Assessments in Study E2023-A001-304: Core Study

Phase	**Prerandomization**	**Randomization**									
Period	**Screening/Baseline**	**Treatment[a]**							**Follow-up[b,c]**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		**ED[d]**	**Unscheduled[e]**
Week	**From –4 Weeks to Week 0**	**0**	**1**	**2**	**4**	**6**	**10**	**14**	**4 weeks after the last dose**		
Procedures/Assessments											
Demography	X										
Informed consent/assent	X										
Inclusion/exclusion criteria	X	X									
Medical history	X										
Epilepsy history[f]	X										
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant AEDs	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Randomization		X									
Study drug compliance			X	X	X	X	X	X		X	X[e,g]
Dispense study drug		X	X	X	X	X	X	X[h]			X[e,g]
Retrieve unused study drug			X	X	X	X	X	X		X	X[e,g]
Dispense subject's diary	X	X	X	X	X	X	X	X[h]			X[e]
Retrieve and review diary		X	X	X	X	X	X	X		X	X[e]
Neurological examination[i]	X							X		X	

Table 3 Schedule of Procedures/Assessments in Study E2023-A001-304: Core Study

Phase	**Prerandomization**	**Randomization**									
Period	**Screening/Baseline**	**Treatment[a]**							**Follow-up[b,c]**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		**ED[d]**	**Unscheduled[e]**
Week	**From –4 Weeks to Week 0**	**0**	**1**	**2**	**4**	**6**	**10**	**14**	**4 weeks after the last dose**		
Procedures/Assessments											
Physical examination[i]	X							X		X	
Vital signs, and weight	X	X	X	X	X	X	X	X		X	X[e]
Height	X										
Clinical laboratory tests[j]	X					X		X		X	X[e,k]
Serum β-hCG test[l]	X										
Urine pregnancy test[l]		X						X		X	X[e]
12-Lead ECG[m]	X							X		X	X[e,k]
Echocardiogram	X							X		X	X[e,k]
PK sampling (plasma)[n]				X	X	X	X			X[o]	
IxRS call	X	X	X	X	X	X	X	X		X	X[e]
C-SSRS	X	X	X	X	X	X	X	X		X	
QoL		X						X		X	
Clinical Global Impression[p]		X						X		X	

AE = adverse event, AED = antiepileptic drug, β-hCG = beta-human chorionic gonadotropin, COVID-19 = Coronavirus disease 2019,
C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, ED = early discontinuation, IxRS = interactive voice and web response system,

Table 3 Schedule of Procedures/Assessments in Study E2023-A001-304: Core Study

Phase	Prerandomization	Randomization									
Period	Screening/Baseline	Treatment[a]							Follow-up[b,c]		
Visit	1	2	3	4	5	6	7	8		ED[d]	Unscheduled[e]
Week	From –4 Weeks to Week 0	0	1	2	4	6	10	14	4 weeks after the last dose		
Procedures/Assessments											

PedsQL = Pediatric Quality of Life Inventory, PK = pharmacokinetic, QoL = Quality of Life in Epilepsy Scale/Pediatric Quality of Life Inventory 4.0; QOLIE-31 = Quality of Life in Epilepsy Survey.

a: All visits to be done within ±3 days of the schedule. If any of the visits after Visit 1 are conducted remotely due to the COVID-19 pandemic, at a minimum, the following assessments should be conducted: AEs, suicidality assessment, concomitant medications, review of seizure diary data, and study drug compliance (any missed or extra doses with dates). Study drug and seizure diary may be picked up from the site by the subject/caregiver or shipped from the site to the subject's location. C-SSRS and Clinical Global Impression may be conducted remotely over the phone by a qualified rater and QOLIE-31 and PedsQL based on input from subject over the phone.

b: Visit to be done within ±7 days of the schedule.

c: The Follow-up Visit only applies to those subjects who do not enter the Extension Phase after completion of this study.

d: These assessments will be conducted for subjects who discontinue the study or treatment early for any reason after Visit 2.

e: At Unscheduled Visits these assessments/procedures conducted if needed.

f: Epilepsy history will include information on genetic mutation related to epilepsy, if available.

g: Unused study drug to be retrieved and study drug dispensed only for subjects requiring dose change at Unscheduled Visits.

h: Study drug and seizure diary will be dispensed only for subjects who enter the Extension Phase.

i: Physical and neurological examinations will only be performed at the indicated visits. For all other clinic visits during the study, the physical and the neurological examinations will only be performed when there is a complaint from the subject. Clinically significant abnormal findings from the physical or the neurological examinations will be reported as AEs.

j: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.

k: At Unscheduled Visits, these assessments will only be done if the results from the previous visit were deemed clinically significant by the investigator.

l: Only for female subjects of child-bearing potential (defined as all postmenarche females, unless postmenopausal or have been sterilized surgically).

m: If subject has a normal ECG baseline reading, but during any visit thereafter the QT is measured as >460 ms, 3 consecutive ECGs separated by 5 to 10 minutes will be performed to confirm the abnormality.

n: One blood sample (approximately 1 mL) for determination of lorcaserin plasma concentrations will be collected at predose and between 1 to 2 hours postdose at Visit 4 and 6; 3 to 6 hours postdose only at Visit 5 and 7.

Table 3 Schedule of Procedures/Assessments in Study E2023-A001-304: Core Study

Phase	**Prerandomization**	**Randomization**									
Period	**Screening/Baseline**	**Treatment[a]**							**Follow-up[b,c]**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**		**ED[d]**	**Unscheduled[e]**
Week	**From –4 Weeks to Week 0**	**0**	**1**	**2**	**4**	**6**	**10**	**14**	**4 weeks after the last dose**		
Procedures/Assessments											

o: At ED Visit, 1 blood sample (approximately 1 mL) PK samples should only be collected only if can be drawn within 50 hours of the last dose of study drug.

p: Clinical Global Impression of Severity is conducted At Visit 2, and Clinical Global Impression of Change at Visit 8 or ED.

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to the Schedule of Procedures/Assessments (Table 3) for procedures/assessments that will be performed during this study.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of epilepsy.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, (or any partner's pregnancy of a male subject in which the estimated date of conception is either before the last visit or within 5 times the half-life of the study drug plus 90 days of last study treatment), or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, a spontaneous abortion or an induced abortion done due to safety concerns for either mother or fetus are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 24 hours from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse and Intentional Overdose, even if asymptomatic, are always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Abnormal Hepatic Tests of Clinical Interest

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."

- Elevated aspartate aminotransferase or alanine aminotransferase laboratory value that is greater than or equal to 3× the upper limit of normal (ULN)

AND

- Elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN

AND AT THE SAME TIME

- Alkaline phosphatase laboratory value that is less than 2× the ULN

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.

9.5.4.3.3 Reporting of Study-Specific Events

The following study-specific AEs should always be considered as SAEs, and entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), as important medical events even if the event does not meet other seriousness criteria:

- Serotonin syndrome (must have at least 1 of the following: spontaneous clonus; inducible clonus PLUS agitation or diaphoresis; ocular clonus PLUS agitation or diaphoresis; tremor PLUS hyperreflexia; hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus)
- Psychosis
- Suicidal behavior

- Priapism
- New or worsened valvular heart disease
- New or worsened pulmonary hypertension
- New arrhythmia or conduction abnormality
- Severe symptomatic hypoglycemia
- Malignant neoplasms

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 3).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, progression of disease, withdrawal of consent (or assent), pregnancy, study terminated by sponsor, or

other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF on a study-phase basis.

A subject removed from the study for any reason may be replaced if the reason for discontinuation is related to the Coronavirus Disease 2019 (COVID-19) pandemic.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF.

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.4.1. Abuse is always to be captured as an AE.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent (or assent) of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding and a snapshot of the database is obtained and released for unblinding. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of Core Study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

- Percent change from baseline in seizure frequency of convulsive seizures per 28 days during the Treatment Period

9.7.1.1.2 SECONDARY ENDPOINTS

Key Secondary Endpoint

- Proportion of 50% responders for convulsive seizures in the Treatment Period

Other Secondary Endpoints

- Proportion of subjects who are free from convulsive seizures in the Treatment Period
- PK parameters of lorcaserin in the Treatment Period
- Safety and tolerability, including incidence of treatment-emergent adverse events (TEAEs)

9.7.1.1.3 EXPLORATORY ENDPOINTS

[redacted]

[redacted]

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

The Full Analysis Set is the group of randomized subjects who received at least 1 dose of study drug and had at least 1 postdose primary efficacy measurement.

The PK Analysis Set is the group of all randomized subjects from whom at least measurable lorcaserin plasma concentration was obtained with associated documented dosing history.

9.7.1.3 Subject Disposition

The number of subjects screened and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the CRF.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Full Analysis Set will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, height, BMI, and weight; categorical variables include sex and race.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Full Analysis Set by Anatomical Therapeutic Chemical class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 28 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

Primary endpoint and other seizure types:

Seizure Frequency: Percent change from baseline in seizure frequency per 28 days for convulsive seizures, total seizures, non-convulsive and per seizure type during the Treatment Period of the Randomization Phase relative to the Prerandomization Phase will be analyzed using rank ANCOVA.

Seizure frequency will be based on number of seizures per 28 days, calculated during the Baseline Period and Treatment Period, as the number of seizures during each respective period divided by the number of non-missing days during each respective period, multiplied by 28. Analysis will be conducted using rank ANCOVA with treatment, fenfluramine and weight stratas, and site as factors, and the baseline seizure frequency as a covariate. In this analysis, all seizure frequency data will be rank transformed first for both baseline and endpoint seizure frequencies separately. The ANCOVA will be conducted based on the rank transformed data. Details will be specified in the SAP.

Due to the expected skewed distribution of seizure frequency, median will be the primary statistics of interest for the primary endpoint, as well as for all other seizure frequency based continuous endpoints.

Sensitivity analysis: Multiple Imputation assuming missing not at random will be used to impute missing data for seizure frequency. Details will be specified in the statistical analysis plan.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

Responder rate: An analysis of subjects who experience a 50% or greater reduction in convulsive seizure frequency in the Treatment Period of the Randomization Phase relative to the Prerandomization Phase will be conducted based on Cochran-Mantel-Haenszel test adjusted for fenfluramine and weight stratas and site.

Sequential Gatekeeping Procedure

In order to control for Type I error, a sequential gatekeeping approach will be used where the primary endpoint will be tested first at 0.05 level, if the null hypothesis is rejected, the key secondary endpoint will be tested at 0.05 significance level. Otherwise no further testing will be performed.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

CCI [redacted]

[redacted]

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 Pharmacokinetic Analyses

Analysis of PK will be performed on the PK Analysis Set. Plasma concentrations of lorcaserin will be listed.

Lorcaserin plasma concentration-time data will be subjected to population PK analysis using nonlinear mixed effects modeling. For this approach, PK analysis data from this study will be pooled with relevant data from other lorcaserin studies as appropriate. The effect of covariates, such as baseline characteristics/demographics, on PK will be explored. Derived exposure parameters such as C_{max} and AUC at steady-state will be calculated from the final PK model using individual posterior estimates of the PK parameters and from dosing history.

Relationships between exposure to lorcaserin and selected efficacy and safety endpoints will be explored graphically if data permits. Any emergent PK/pharmacodynamic relationship will be followed by population PK/pharmacodynamic modeling if data allow.

9.7.1.7.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Data may be analyzed based on types of genetic mutations related to epilepsy.

9.7.1.8 Safety Analyses

Safety analyses will be conducted on the Safety Analysis Set. The data will be summarized by overall, treatment group, and by age group.

The incidence of TEAEs, SAEs, AEs leading to discontinuation of study drug, and AEs leading to dose adjustment will be summarized. The incidence of TEAEs will be summarized by severity (mild, moderate, or severe), as well as by relationship to treatment (related or not related). Proportion of subjects with increased seizure frequency, weight and BMI changes will be summarized.

The change from baseline in vital signs and ECG parameters will be summarized, and changes from baseline in laboratory values will be summarized for continuous variables.

Incidence of FDA-defined valvulopathy and pulmonary hypertension, and change from baseline of echocardiographic parameters will be summarized. Incidence of bradycardia,

new onset heart block, new onset of other arrhythmias or conduction abnormalities, thickened valve leaflets, and restricted valve leaflet motion will be summarized.

Proportion of subjects with any treatment-emergent study-specific AEs will be summarized.

9.7.1.8.1 EXTENT OF EXPOSURE

The duration of treatment will be calculated as the number of days between the date the subject receives the 1st treatment dose and the date the subject receives the last dose of treatment. These values will be used to summarize the extent of exposure to study drug.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 23 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

The number (percentage) of subjects with TEAEs leading to treatment dose adjustment will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to treatment dose adjustment will be provided.

9.7.1.8.3 LABORATORY VALUES

Changes from baseline in laboratory values will be summarized for continuous variables. Laboratory shift tables showing incidence of new or worsening clinically significant findings from baseline to the postbaseline visits will be displayed. Shift from baseline to the highest postbaseline laboratory value and from baseline to the lowest postbaseline laboratory value will also be displayed.

Incidence of treatment-emergent markedly abnormal laboratory values in laboratory safety test variables will be summarized. Treatment-emergent markedly abnormal laboratory values will be graded based on the Common Terminology Criteria for Adverse Events Version 5.0. Incidence of Hy's law will be summarized.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed at Unscheduled, if needed (See Table 3). Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group.

9.7.1.8.6 OTHER SAFETY ANALYSES

The proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors will be summarized.

Listings from pregnancy tests will be prepared.

9.7.1.9 Other Analyses

The change from baseline in QOLIE-31 and PedsQL 4.0 Scale will be summarized.

9.7.2 Determination of Sample Size

A sample size of 58 subjects (29 per group) will have 90% power to detect a difference of 50% reduction in convulsive seizure frequency per 28 days between lorcaserin and placebo assuming a standard deviation of 55, using a 2-group t-test with 0.05 two sided significance level. This sample size will have 90% power to detect an odds-ratio of at least 10 for the secondary endpoint 50% reduction in convulsive seizure frequency, assuming the placebo response is 12%, using a 2-group Chi-square test with 0.05 two-sided significance level. This sample size assumes a 7% dropout rate. Sample size was estimated based on the percent reduction of convulsive seizures and standard deviation reported in fenfluramine study in Dravet syndrome (Lagae et al., 2020).

9.7.3 Interim Analysis

No interim analysis is planned.

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB, but the health or regulatory authority and IRB (if applicable) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB (if applicable) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following items, the data recorded directly on the CRF are to be considered source data:

- Reasons for discontinuation of study treatment
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)
- Reasons for dose modification
- Indication for prior/concomitant medication

- Sampling times for drug concentrations
- Sampling times for clinical laboratory tests.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 15 years following the completion of the study.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB and provide the sponsor and the IRB with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum – low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
ALT	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
AST	>ULN – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 5.0×ULN if baseline was normal; 3.0 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0×baseline if baseline was abnormal
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN if baseline was normal; 1.0 – 1.5×baseline if baseline was abnormal	>1.5 – 3.0×ULN if baseline was normal; 1.5 – 3.0×baseline if baseline was abnormal	>3.0 – 10.0×ULN if baseline was normal; 3.0 – 10.0×baseline if baseline was abnormal	>10.0×ULN if baseline was normal; >10.0×baseline if baseline was abnormal
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L Ionized calcium <LLN – 1.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L Ionized calcium <1.0 – 0.9 mmol/L; symptomatic	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L Ionized calcium <0.9 – 0.8 mmol/L; hospitalization indicated	<6.0 mg/dL <1.5 mmol/L Ionized calcium <0.8 mmol/L; life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L Ionized calcium >ULN – 1.5 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L Ionized calcium >1.5 – 1.6 mmol/L; symptomatic	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L Ionized calcium >1.6 – 1.8 mmol/L; hospitalization indicated	>13.5 mg/dL >3.4 mmol/L Ionized calcium >1.8 mmol/L; life-threatening consequences
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×baseline; >1.5 – 3.0×ULN	>3.0×baseline; >3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 2.5×ULN if baseline was normal; 2.0 – 2.5×baseline if baseline was abnormal	>2.5 – 5.0×ULN if baseline was normal; >2.5 – 5.0×baseline if baseline was abnormal	>5.0 – 20.0×ULN if baseline was normal; >5.0 – 20.0×baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0× baseline if baseline was abnormal
Glucose, serum-high (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	life-threatening consequences; urgent intervention indicated
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L; life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L; intervention initiated	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	125 – 129 mmol/L and asymptomatic	<125 – 129 mmol/L symptomatic; 120 – 124 mmol/L regardless of symptoms	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Uric acid, serum-high (hyperuricemia)	>ULN without physiologic consequences	N/A	>ULN with physiologic consequences	life-threatening consequences

Based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: 27 Nov, 2017.
ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.

Appendix 2 Extension Phase

Study Design and Plan

The Extension Phase will consist of a Treatment Period (12 weeks) and a Follow-up Period (4 weeks). Subjects are eligible to complete the Extension Phase only if they have completed the Treatment Period of the Core Study.

All subjects will receive lorcaserin during entire Extension Phase but the dose level will be blinded during the first 6 weeks. During the first 6 weeks of the Extension Phase, subjects who received lorcaserin during the Core Study will receive the same dose of lorcaserin (the dose will remain flexible per weight category, based on clinical response and tolerability); subjects who received placebo during the Core Study will receive the target dose of lorcaserin per weight category. During the second 6 weeks of the Extension Phase, all subjects will receive lorcaserin at the maximum dose per weight category (the dose may be decreased due to tolerability reasons and increased again if tolerability improves). Addition, deletion, and dose changes to concomitant antiepileptic drugs (AEDs) are not allowed during the Treatment Period of the Extension Phase.

The Follow-up Visit will be conducted 4 weeks after the last dose of study drug for subjects who will not participate in the Extended Access Program (Study E2023-A001-405) after completion of this study.

The objectives of the Extension Phase are:

- To evaluate the safety and tolerability of lorcaserin
- To characterize the pharmacokinetics (PK) of lorcaserin and the relationship between lorcaserin plasma concentrations, efficacy, and safety
- To summarize the efficacy of lorcaserin as measured by percent change in frequency of convulsive seizures
- To summarize the efficacy of lorcaserin as measured by percent change in frequency of each type of seizure
- To summarize the efficacy of lorcaserin as measured by proportion of subjects who are free from convulsive seizures
- To summarize the efficacy of lorcaserin as measured by proportion of subjects who are seizure-free
- To summarize the efficacy of lorcaserin as measured by percent change in frequency of clusters
- To summarize the efficacy of lorcaserin as measured by Clinical Global Impression of Change
- To summarize the efficacy of lorcaserin as measured by on quality of life

Schedule of Procedures/Assessments

Table 4 presents the Schedule of Procedures/Assessments for the Extension Phase.

Table 4 Schedule of Procedures/Assessments in Study E2023-A001-304: Extension Phase

Phase	**Extension**							
Period	**Treatment[a]**					**Follow-up[b,c]**		
Visit	**9**	**10**	**11**	**12**	**13**		**ED[d]**	**Unscheduled[e]**
Week	**15**	**17**	**20**	**23**	**26**	**4 weeks after the last dose**		
Procedures/Assessments								
Prior and concomitant medications	X	X	X	X	X	X	X	X
Prior and concomitant AEDs	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Study drug compliance	X	X	X	X	X		X	X[e,f]
Dispense study drug	X	X	X	X				X[e,f]
Retrieve unused study drug	X	X	X	X	X		X	X[e,f]
Dispense subject's diary	X	X	X	X				X[e]
Retrieve and review diary	X	X	X	X	X		X	X[e]
Neurological examination[g]					X		X	
Physical examination[g]					X		X	
Vital signs, and weight	X	X	X	X	X		X	X[e]
Clinical laboratory tests[h]					X		X	X[e,i]
Urine pregnancy test[j]					X		X	X[e]
12-lead ECG[k]					X		X	X[e,i]
IxRS call	X	X	X	X	X		X	X[e]
C-SSRS	X	X	X	X	X		X	
QoL					X		X	

Table 4 Schedule of Procedures/Assessments in Study E2023-A001-304: Extension Phase

Phase	**Extension**							
Period	**Treatment[a]**					**Follow-up[b,c]**		
Visit	**9**	**10**	**11**	**12**	**13**		**ED[d]**	**Unscheduled[e]**
Week	**15**	**17**	**20**	**23**	**26**	**4 weeks after the last dose**		
Procedures/Assessments								
Clinical Global Impression[l]					X[l]		X	
PK Sampling (plasma)[m]	X	X	X	X	X		X[n]	

AE = adverse event, AED = antiepileptic drug; COVID-19 = Coronavirus disease 2019, C-SSRS = Columbia-Suicide Severity Rating Scale, ECG = electrocardiogram, ED = early discontinuation, IxRS = interactive voice and web response system, PedsQL = Pediatric Quality of Life Inventory, QoL = Quality of Life in Epilepsy Scale/Pediatric Quality of Life Inventory 4.0, QOLIE-31 = Quality of Life in Epilepsy Survey.

a: All visits to be done within ±3 days of the schedule. If any of the visits after Visit 1 are conducted remotely due to the COVID-19 pandemic, at a minimum, the following assessments should be conducted: AEs, suicidality assessment, concomitant medications, review of seizure diary data, and study drug compliance (any missed or extra doses with dates). Study drug and seizure diary may be picked up from the site by the subject/caregiver or shipped from the site to the subject's location. C-SSRS and Clinical Global Impression may be conducted remotely over the phone by a qualified rater and QOLIE-31 and PedsQL based on input from subject over the phone.

b: Visit to be done within ±7 days of the schedule.

c: The Follow-up Visit only applies to those subjects who do not participate in the Extended Access Program (Study E2023-A001-405) after completion of this study.

d: These assessments will be conducted for subjects who discontinue the study or treatment early for any reason after Visit 9.

e: At Unscheduled Visits these assessments/procedures conducted if needed.

f: Unused study drug to be retrieved and study drug dispensed only for subjects requiring dose change at Unscheduled Visits.

g: Physical and neurological examinations will only be performed at the indicated visits. For all other clinic visits during the study, the physical and the neurological examinations will only be performed when there is a complaint from the subject. Clinically significant abnormal findings from the physical or the neurological examinations will be reported as AEs.

h: Clinical laboratory tests include hematology, blood chemistry, and urinalysis.

i: At Unscheduled Visits, these assessments will only be done if the results from the previous visit were deemed clinically significant by the investigator.

j: Only for female subjects of child-bearing potential (defined as all postmenarche females, unless postmenopausal or have been sterilized surgically).

k: If subject has a normal ECG baseline reading, but during any visit thereafter the QT is measured as >460 ms, 3 consecutive ECGs separated by 5 to 10 minutes will be performed to confirm the abnormality.

Table 4 Schedule of Procedures/Assessments in Study E2023-A001-304: Extension Phase

Phase	**Extension**							
Period	**Treatment[a]**					**Follow-up[b,c]**		
Visit	**9**	**10**	**11**	**12**	**13**		**ED[d]**	**Unscheduled[e]**
Week	**15**	**17**	**20**	**23**	**26**	**4 weeks after the last dose**		
Procedures/Assessments								

l: Clinical Global Impression of Change at Visit 13 or ED.

m: One blood sample (approximately 1 mL) for determination of lorcaserin plasma concentration will be collected at predose and between 1 to 2 hours postdose at Visit 9, 11, and 13; 3 to 6 hours postdose only at Visit 10 and 12.

n: At ED, 1 blood sample (approximately 1 mL) PK samples should be collected only if samples can be drawn within 50 hours of the last dose of study drug.

Statistical Methods

Statistical analyses will be performed by the sponsor or designee after the study is completed, the database is locked and released, and a snapshot of the database is obtained and released. Analyses for regional submissions may be performed during the course of the study. Statistical analyses will be performed using SAS software or other validated statistical software, as required. Details of the statistical analyses will be included in a separate statistical analysis plan.

Statistical and Analytical Plans

The statistical analyses of Extension Phase data are described in this section. Further details of the analytical plan will be provided in the statistical analysis plan, which will be finalized before database lock and treatment unblinding.

Study Endpoints

- Safety and tolerability, including incidence of treatment-emergent adverse events
- PK parameters of lorcaserin in the Treatment Period
- Percent change in frequency of convulsive seizures
- Percent change in frequency of each type of seizure
- Proportion of subjects who are free from convulsive seizures
- Proportion of subjects who are seizure-free
- Percent change from baseline in frequency of clusters
- Clinical Global Impression of Change
- Change from baseline in QOLIE-31 and PedsQL 4.0 Scales

Analysis sets

Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment in the Extension Phase.

Full Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose seizure measurement in the Extension Phase.

Efficacy Analyses

Descriptive statistics will be provided for the efficacy endpoints in the Extension Phase. Mean, standard deviation, median, minimum, and maximum will be provided for continuous endpoints and number and percentage will provide for categorical variables. In addition, plots will be used to summarize the data.

Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data that will be evaluated include monitoring and recording all adverse events; regular laboratory evaluation for hematology, blood chemistry, and urinalysis; periodic measurement of vital signs, weight and ECGs; and the performance of physical and neurological examinations. Safety analyses will be performed similarly to the Core Study analyses and all analyses will be on the treatment duration (Core Study and Extension Phase).

Appendix 3 Scheme of IxRS Study Drug Assignment and Preparation of Study Drug Suspension

Table 5 Scheme of IxRS Study Drug Assignment and Preparation of Study Drug Suspension

Weight Group	Daily Dose	Dose per Administration	Volume of Suspension per Administration	Volume of Water	Volume of Ora-Sweet Syrup	Tablet A	Weight Group
10 to <20 kg	Placebo	Placebo	20 mL	10 mL	70 mL	Placebo 1 tablet	Placebo 1 tablet
10 to <20 kg	5 mg	2.5 mg	20 mL	10 mL	70 mL	10 mg 1 tablet	Placebo 1 tablet
10 to <20 kg	10 mg	5 mg	20 mL	10 mL	70 mL	10 mg 1 tablet	10 mg 1 tablet
20 to <40 kg	Placebo	Placebo	40 mL	10 mL	70 mL	Placebo 1 tablet	Placebo 1 tablet
20 to <40 kg	10 mg	5 mg	40 mL	10 mL	70 mL	10 mg 1 tablet	Placebo 1 tablet
20 to <40 kg	20 mg	10 mg	40 mL	10 mL	70 mL	10 mg 1 tablet	10 mg 1 tablet
≥40 kg	Placebo	Placebo	40 mL	10 mL	70 mL	Placebo 1 tablet	Placebo 1 tablet
≥40 kg	20 mg	10 mg	40 mL	10 mL	70 mL	10 mg 1 tablet	10 mg 1 tablet

IxRS = interactive voice and web response system

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2023-A001-304
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of Lorcaserin as Adjunctive Treatment in Subjects with Dravet Syndrome
Investigational Product Name:	E2023/lorcaserin
IND Number:	148085

SIGNATURES

Authors:

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Clinical Pharmacologist
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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2023-A001-304
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study with Open-Label Extension Phase of Lorcaserin as Adjunctive Treatment in Subjects with Dravet Syndrome
Investigational Product Name:	E2023/lorcaserin
IND Number:	148085

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date