Version 4.0, 18 May 2024

Change	Rationale
Section 3.2 Added "The study is planned to be conducted in US, Canada, India, and China or Brazil (to be determined)." to describe the regions	The study will be expanded to new regions
Section 3 and Section 4 Updated the number of randomized subjects to achieve target number of subjects in the Full Analysis Set	To account for a higher drop-out rate assumption
Section 3.2 Added "centralized" to describe the randomization	Previously there was only one region, so we did not need to specify whether randomization was centralized or not as that was the only choice. In the current version, there are multiple regions. We added "centralized" to describe the type of randomization and to differentiate it from conducting randomization within each region. Centralized randomization is chosen because it controls the imbalance in treatment allocation in the overall population better compared to randomization within each region.
Section 5.2.4 Added region to demographic characteristics	Region added since the study will be expanded to new regions
Section 5.3 (Section 4.6.1 in the original version) Removed "4.6.1 Pooling of Centers This is a multicenter study to be conducted in the US and Canada. Decisions regarding pooling of data across sites that had low enrollment will be made and documented before treatment unblinding."	Region, instead of site, will be included in analysis model
Section 5.3.1 Deleted "a" before "covariates"	Typographical correction
Section 5.3.1 Added "Other covariates include region, baseline seizure frequency, and treatment-by-region interaction."	To account for new regions in analysis model
Section 5.3.3 Add "key secondary endpoint" for subgroup analysis	To perform sensitivity analysis for key secondary endpoint as well
Section 5.3.3 Replace "site" by "Region (US and Canada, India, and China/Brazil)"	Replace site by region since some sites may enroll one or two subjects
Section 5.3.3 Replace "Epilepsy syndrome" by "Seizure types"	To correct an inadvertent error.
Section 5.4.1 Updated efficacy analysis methodology to include region and treatment-by-region interaction as factors in the rank ANCOVA	To adjust for potential sources of heterogeneity in analysis model

Section 5.4.2 Updated key secondary efficacy analysis to adjust for region in Cochran-Mantel-Haenszel test	To adjust for potential sources of heterogeneity in Cochran-Mantel-Haenszel test
Section 5.8 Added region to exploratory analysis model and test	To adjust for potential sources of heterogeneity in analysis model and test
Section 7 Added "The sponsor has decided to terminate this study. With 22 subjects randomized, which represents for 35% of the planned number, only descriptive statistics for primary, secondary, and selected exploratory endpoints will be provided. Subgroup analysis will be limited to seizure type, while sensitivity analysis will not be conducted. Given the limited PK data, we will only provide summary statistics for plasma concentrations of lorcaserin. We will not derive steady-state PK parameters such as C_{max} and AUC, nor to explore relationships between exposure to lorcaserin and selected efficacy and safety endpoints."	To explain the changes in the planned analyses resulting from the study termination.
Section 9 Added region to SAS code step 2 and 3	To adjust for potential sources of heterogeneity in analysis model and imputation model
Updated the SAP signature page	Administrative change

Version 1.0, 26 Jun 2020

Change	Rationale
Section 2 Added additional fenfluramine stratification to the description of randomization, "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)."	Subjects previously treated with fenfluramine strata needs be balance by randomization.
Added fenfluramine strata to Section 4.6.2 Adjustment of Covariates and Section 4.6.4 Examination of Subgroups	Fenfluramine strata added since randomization stratification was change.
Section 4.9.1; added fenfluramine strata to primary analysis model	Fenfluramine strata added since randomization stratification was change.
Section 4.13 added fenfluramine strata to exploratory analysis model	Fenfluramine strata added since randomization stratification was change.
Section 2 added "The stratification factors will be balance between treatment groups using restricted randomization method proposed by Pocock and Simon (1975)." in the 4th paragraph	As per FDA suggestion
Section 4.6.1 Added "Canada"	In order to help with recruitment Canadian sites were added.
Section 4.91. The primary model was simplified. Two and three way interactions were removed. In addition, site was removed from the model due to some sites only contributing 1 to 2 subjects.	As suggested by FDA
Section 4.9.2 fenfluramine strata added to CMH test and site remove.	As suggested by FDA
Section 9: fenfluramine strata was added to multiple imputation models. Site was deleted from imputation models	Added fenfluramine strata as a randomization strata. Site is deleted since some sites may enroll one or two subjects. This may cause multiple simulations to not converge.

STATISTICAL ANALYSIS PLAN

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
Date:	18 May 2024
Version:	Final Version 4.0

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACMV	available cases missing value
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic class
BOCF	baseline observation carried forward
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
FAS	full analysis set
FCS	Fully Conditional Specification
LOCF	last observation carried forward
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MNAR	Missing not at Random
PD	pharmacodynamic
PK	pharmacokinetic
PMM	Predictive Mean Matching
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SI	Système International
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
US	United States
WHO	World Health Organization

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E2023-A001-304.

3.1 Study Objectives

3.1.1 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.

3.1.2 Secondary Objectives

3.1.2.1 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).

3.1.2.2 Other Secondary Objective

- 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

3.1.3 Exploratory Objective(s)

[redacted]

3.2 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 is planned to be conducted in US, Canada, India, and China or Brazil (to be determined). 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 62 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 centralized and stratified by previous treatment with fenfluramine (yes, no) and by weight categories (10 to <20 kg, 20 to <40 kg, and ≥40 kg). The stratification factors will be balanced between treatment groups using restricted randomization method proposed by Pocock and Simon (1975).

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 category at randomization, as described in Section 9.4.1 of the protocol.

For lower weight categories, during the first 2 weeks of Treatment Period, 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 of the protocol). 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.

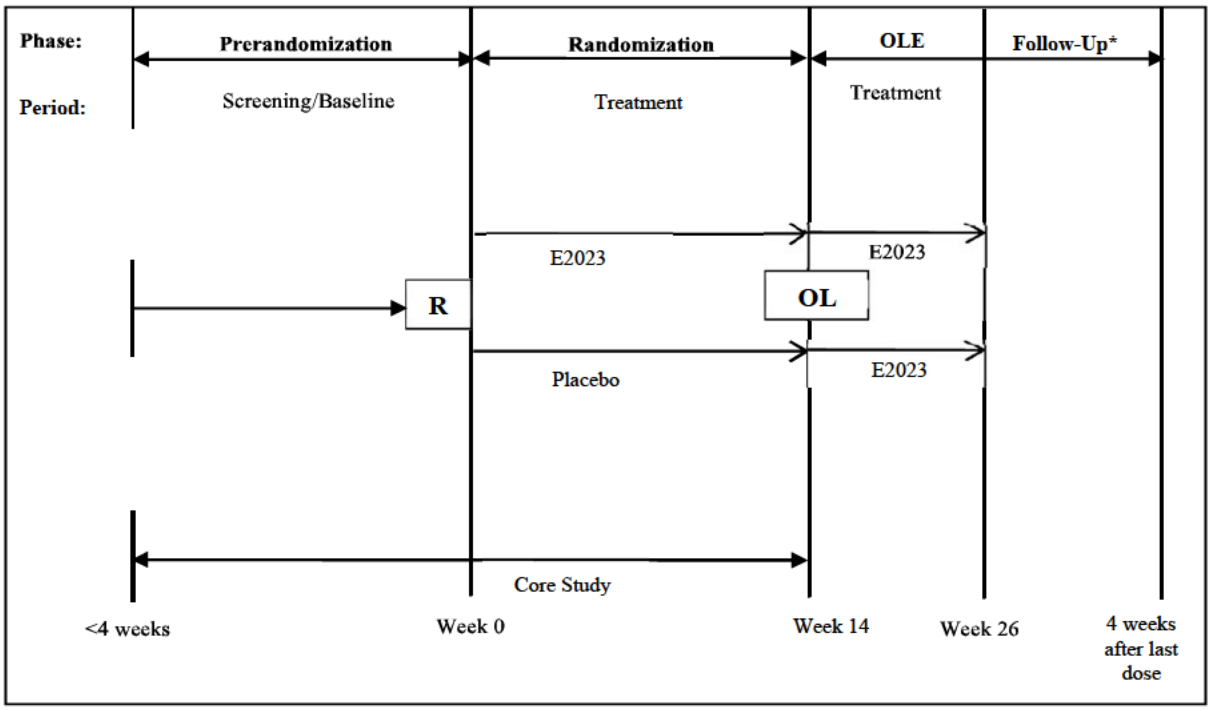

Figure 1 Study Design: E2023-A001-304 Core Study and Extension Phase

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.

4 DETERMINATION OF SAMPLE SIZE

A sample size of 54 subjects (27 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. 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). Approximately 62 subjects will be randomized assuming a dropout rate of 12%.

5 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.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

5.1 Study Endpoints

5.1.1 Primary Endpoint

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

5.1.2 Key Secondary Endpoint

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

5.1.3 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)

5.1.4 Exploratory Endpoints

5.2 Study Subjects

5.2.1 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.

5.2.2 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.

5.2.3 Protocol Deviations

Major protocol deviations will be summarized by number (percentage). In addition, a subject listing will be provided along with the description of the protocol deviation. Protocol deviations will be identified prior to database lock.

5.2.4 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, race, and region.

MEDICAL HISTORY

The number (percentage) of subjects in the Full Analysis Set reporting a history of any medical condition, as recorded on the CRF, will be summarized for each treatment group and overall. A subject data listing of medical and surgical history will be provided.

5.2.5 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 the subject's last dose or 28 days after the subject's last dose for subjects who do not enter the extension phase (for core study analysis) or do not enter Study E2023-A001-405 (for extension phase analysis). All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Overall compliance rate will be determined and defined as the difference in the tablets dispensed minus the number of tables returned, divided by the expected number of tablets to be taken, multiplied by 100. Descriptive statistics (n, mean, standard deviation, median minimum, maximum) and number (percentage) of subjects in compliance categories (<50%, 50 to <80%, 80 to ≤120%, >120%) will be provided for the entire double-blind core phase. The Safety Analysis Set will be used.

5.3 Data Analysis General Considerations

5.3.1 Adjustments for Covariates

In the statistical models, the randomization stratification variables for fenfluramine (yes, no) and weight categories (10 to <20 kg, 20 to <40 kg, and ≥40 kg) will be included as covariates. Other covariates include region, baseline seizure frequency, and treatment-by-region interaction.

5.3.2 Multiple Comparisons/Multiplicity

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.

5.3.3 Examination of Subgroups

The primary endpoint and key secondary endpoint will be summarized using descriptive statistics by each subgroup listed below. No hypothesis testing will be performed in the subgroup analyses.

- Age group (≥ 2 to <12 yrs, ≥12 yrs)
- Sex (male and female)
- Race (white, black, Asian, and other)
- Region (US and Canada, India, and China/Brazil)
- Weight Strata (10 to <20 kg, 20 to <40 kg, and ≥40 kg)
- Fenfluramine strata (yes, no)
- Prior to drug interruption, during drug interruption and after drug interruption
- Seizure types

Additional subgroup analyses may also be conducted, if deemed appropriate.

5.3.4 Handling of Missing Data, Dropouts, and Outliers

The primary efficacy endpoint, percent change from baseline in convulsive seizures, will be analyzed using rank ANCOVA model. Seizure frequency for convulsive seizures will be based on number of seizures per 28 days, calculated during the Baseline Period and Double-blind 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. Additional sensitivity analysis will be performed using multiple imputation (MI) assuming missing not at random (MNAR) to impute missing weeks on the primary efficacy endpoint as follows:

Table 1 Multiple Imputation Method

<table>
<tr><th>MI Methods</th><th>Assumption</th></tr>
<tr><td>Available Case Missing Value</td><td>This MI method will use all available monotone missing patterns to impute missing data assuming MNAR.
<table>
<tr><th>Visit</th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>6</th><th>7</th><th>8</th></tr>
<tr><th>Week</th><th>Screening</th><th>0</th><th>1</th><th>2</th><th>4</th><th>6</th><th>10</th><th>14</th></tr>
<tr><th>Pattern</th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></tr>
<tr><td>1</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>2</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>.</td></tr>
<tr><td>3</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>.</td><td>.</td></tr>
<tr><td>4</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td>.</td><td>.</td><td>.</td></tr>
<tr><td>5</td><td>X</td><td>X</td><td>X</td><td>X</td><td>.</td><td>.</td><td>.</td><td>.</td></tr>
<tr><td>6</td><td>X</td><td>X</td><td>X</td><td>.</td><td>.</td><td>.</td><td>.</td><td>.</td></tr>
<tr><td>7</td><td>X</td><td>X</td><td>.</td><td>.</td><td>.</td><td>.</td><td>.</td><td>.</td></tr>
<tr><td>8</td><td>X</td><td>.</td><td>.</td><td>.</td><td>.</td><td>.</td><td>.</td><td>.</td></tr>
<tr><td colspan="9">X=observed data; .=missing data</td></tr>
</table></td></tr>
</table>

The MI algorithm is described in Section 5.4.1 and SAS pseudo program code is found Section 9.

5.3.5 Other Considerations

The following estimands are evaluated for the primary efficacy endpoint, percent change from baseline in seizure frequency per 28 days in convulsive seizures, and key secondary endpoint, 50% reduction of convulsive seizures per 28 days.

Table 2 Estimands for Primary and Key Secondary Endpoints				
Estimand	**Description**	**Population**	**Intervention Effect of Interest**	**Analysis Type**
Difference in outcomes	all randomized subjects regardless of the treatment subjects actually received; subjects with any observed data	FAS	Seizure frequency for convulsive seizures 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	Primary Endpoint
Difference in outcomes	all randomized subjects regardless of the treatment subjects actually received	FAS	Missing values imputed using MI assuming MNAR utilizing ACMV missing value pattern (all available up to 8 monotone missing patterns). Assume the probability of missing observations for any subject depends on the unobserved events. The distribution at each visit is a weighted sum of complete cases. Up to 8 monotone missing patterns will be used in the imputation. See Table 1.	Sensitivity to Primary Endpoint
Difference in outcomes	all randomized subjects regardless of the treatment subjects actually received	FAS	50% Reduction will be derived from the primary endpoint	Key Secondary Endpoint
Difference in outcomes	all randomized subjects regardless of the treatment subjects actually received	FAS	50% Reduction will be derived from MI data based on the sensitivity analysis of primary endpoint	Sensitivity to Key Secondary Endpoint

5.4 Efficacy Analyses

Seizure frequency for convulsive seizures, total seizures, non-convulsive and per seizure, 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.

5.4.1 Primary Efficacy Analysis

Percent change from baseline in seizure frequency per 28 days for convulsive seizures will be analyzed using rank ANCOVA with treatment, fenfluramine, weight, and region strata, and treatment-by-region interaction 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 period and treatment period seizure frequencies separately. The median percent change from baseline and the 95% confidence interval (CI) will be calculated within treatment groups and for comparison of treatment groups (lorcaserin vs. placebo).

Null Hypothesis: No difference exists in the percent mean change from Baseline in convulsive seizures of treatment with lorcaserin as compared with PBO.

Alternative Hypothesis: A difference exists in the percent mean change from Baseline in convulsive seizures for lorcaserin as compared with PBO.

5.4.1.1 Multiple Imputation

Prior to MI, seizure frequency will be log-tranformed in order to assume a multivariate log-normal distribution.

Step 1 (imputing missing data): Thirty multiple imputed complete datasets were to be constructed using imputation regression model of age, weight, day1 to day98 (or last day of double-blind phase) with a predefined arbitrary seed number (seed = 2023). The dataset will be converted into monotone missing pattern by imputing arbitrary missing data as the first step. The monotone data will then be imputed with monotone Fully Conditional Specification (FCS) predictive mean matching (PMM) regression method with neighbor size (k=5) and MNAR.

The thirty complete imputed datasets will be back transformed by exponentiation of the log- transformed data. The sample SAS statements can be found in Section 9.

Step 2 (performing rank ANCOVA using each imputed dataset): For each of the thirty imputed datasets the seizure frequency per 28 days for the Baseline Period and Treatment Period will be derived and the percent change from baseline will be determined. The rank ANCOVA model for the primary efficacy analysis will be used on each of the thirty imputed datasets. SAS PROC MIXED will be used. The sample SAS statement can be found in Section 9.

Step 3 (combine results): Resulting treatment effect parameter estimators and standard errors from each of 30 multiple imputed datasets from Step 2 will be combined using SAS PROC MIANALYZE to obtain the pooled treatment effect and variance parameter estimators according to Rubin's rules (Rubin DB, 1987). The sample SAS statement can be found in Section 9.

5.4.2 Key Secondary Efficacy Analysis

Proportions of subjects who experience a 50% or greater reduction in convulsive seizure frequency in the Treatment Period relative to the Baseline Period will be conducted based on Cochran-Mantel-Haenszel test and 95% CI, adjusted for fenfluramine, weight, and region strata.

5.4.3 Other Efficacy Analyses

No other efficacy analyses are planned for this study.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Details of the analysis methods for population PK/PD modeling will not be described in this SAP but will be described in a separate analysis plan.

5.5.1 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.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

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

5.6 Safety Analyses

Safety analyses will be conducted on the Safety Analysis Set. The data will be summarized by overall, treatment group, using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [percentage] for categorical variables).

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,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.

5.6.1 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.

5.6.2 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 up to the subject's last dose or up to 28 days after the subject's last dose for subjects who do not enter the extension phase (for core study analysis) or do not enter Study E2023-A001-405 (for extension phase analysis), 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.

Adverse events will be summarized by the following subgroups: age (≥ 2 to <12 yrs, ≥12 yrs), sex (male, female), and race (white, black, other).

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in protocol Section 9.5.1.4.4. Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in protocol Section 9.5.1.4.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will be used to compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

The Sponsor's Grading for Laboratory Values (see Section 13, Appendix 13.1) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable. Incidence of Hy's law will be summarized.

5.6.4 Vital Signs

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

5.6.5 Electrocardiograms

ECG assessments will be performed at Unscheduled visit, if needed. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Proportion of subjects with New FDA-defined valvulopathy will be summarized by visit and treatment group.

5.6.6 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.

5.7 Other Analyses

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

5.8 Exploratory Analyses

[redacted]

5.9 Extension Phase Analyses

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. Efficacy analyses will be performed similarly to the Core Study analyses and all analyses will be on the treatment duration (Core Study and Extension Phase).

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).

6 INTERIM ANALYSES

No interim analysis is planned.

7 CHANGES IN THE PLANNED ANALYSES

The sponsor has decided to terminate this study. With 22 subjects randomized, which represents for 35% of the planned number, only descriptive statistics for primary, secondary, and selected exploratory endpoints will be provided. Subgroup analysis will be limited to seizure type, while sensitivity analysis will not be conducted.

Given the limited PK data, we will only provide summary statistics for plasma concentrations of lorcaserin. We will not derive steady-state PK parameters such as C_{max} and AUC, nor to explore relationships between exposure to lorcaserin and selected efficacy and safety endpoints.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Efficacy: Seizure Frequency per 28 Days

Seizure frequency for convulsive seizures, total seizures, non-convulsive seizures, and per seizure type, 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.

Baseline Period Seizure Frequency: number of seizures during the screening period to the date prior to randomization, divided by the number of non-missing days, multiplied by 28.

Treatment Period Seizure Frequency: number of seizures from the date of randomization to the end of the treatment period divided by the number of non-missing days, multiplied by 28.

Endpoint Definitions:

Percent Change from Baseline = 100 * (Treatment Period – Baseline Period) / Baseline Period

For the rank ANCOVA models the ranks of Baseline Period Seizure Frequency and the ranks of Percent Change from Baseline will be used in the analyses.

50% Responders = 1 if percent change from baseline ≤ -50%
0 otherwise

Seizure freedom for convulsive seizures, non-convulsive seizures, and total seizures, will be defined two ways; 1) counting seizures only and not counting clusters and 2) counting both seizures and clusters

Seizure-freedom = 1 if percent change from baseline = -100%
0 otherwise

Convulsive seizures: The sum of seizure frequencies of hemiclonic, tonic, clonic, tonic-atonic, generalized tonic-clonic, and focal with clearly observable motor signs.

Non-convulsive seizures: The sum of all other seizure frequencies not listed under convulsive seizures.

Total seizures: The sum of seizure frequencies for all seizure types.

S-curve plots (percent change from baseline on the x-axis and cumulative proportion on the y-axis) both treatment groups, will be provided for convulsive seizures, non-convulsive seizures and total seizures.

8.2 Safety

Baseline is the last safety assessment prior to the date of randomization.

Adverse Events and Concomitant Medications:

Adverse events with missing severity will be assigned the highest severity. Adverse events with missing relationship will be assigned as related, as part of a sensitivity analysis. Adverse events and Concomitant Medications with partial dates will be imputed according to the algorithm defined in the SDTM specifications.

Treatment Compliance:
Treatment compliance will be determined for the entire double blind treatment period. The total tablets taken = total tablets dispensed – total tablets returned. Compliance = 100 x Total tablets taken / Total tablets Expect

Echocardiogram:

The aortic and mitral valve regurgitation will be categorized as absent, trace, mild, moderate or severe. FDA-defined valvulopathy, or simply "FDA valvulopathy," stipulate that significant valvular regurgitation comprises **mild or greater aortic valve regurgitation and/or moderate or greater mitral valve regurgitation**. The ECHO data presents the mitral and aortic valve severity as 5 categories; ABSENT, TRACE, MILD, MODERATE, and SEVERE.

For each subject and visit a dichotomous variable will be created, where;

1 = mild or greater aortic valve regurgitation and/or moderate or greater mitral valve Regurgitation

0 = aortic valve regurgitation is absent or trace and mitral valve regurgitation is mild or less.

8.3 Definition of Visit Windows

Table 3 of the protocol presents the schedule of procedures/Assessments. The screening/baseline period is four weeks long and procedures/assessments are performed at randomization, weeks 1, 2, 4, 6, 10, and 14 of the treatment period with a follow-up of 4 weeks after end of treatment. Table 3 presents the protocol specified visits/weeks and corresponding time windows used for visit-wise analyses are presented in terms of days relative to the randomization. If more than one measurement is included in a visit window, the measurement collected closest to the scheduled date will be used in the analysis. In the case where two measurements were collected an equal number of days before and after the Scheduled Day the later of the two measurements will be used for analysis. For ECHO assessments when assessing a new or worsened event then the most severe assessment will be selected if 2 or more assessments fall within a visit window

Table 3 Visit Windows Measurements

Scheduled	Scheduled Week	Scheduled	Time Window (Days)	
1	Screening		First day of Screening	-1
2	Baseline/ Randomization	1	1	
3	1	7	2	10
4	2	14	11	17
5	4	28	18	34
6	6	42	35	48
7	10	70	49	82
8	14	98	83	101
Extension Phase				
9	15	105	102	110
10	17	119	111	125
11	20	140	126	149
12	23	161	150	169
13	26	182	170	194

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

The following SAS pseudo code is to outline the algorithm for using multiple imputation methodology under missing not at random (MNAR) assumption for imputing missing data for the primary endpoint seizure frequency, during the double-blind period.

The following covariates will be used in the imputation models.

Step 1: Impute arbitrary missing days and create dataset into monotone missing patterns

PROC MI data=<dataset> nimpute=30 seed=2023 out=<dataset1>;
MCMC chain=multiple nbiter=500 niter=300 impute=monotone;
VAR age weight log(day1) - log(day98 or last day of double-blind phase);
BY treatment;
RUN;

- Exponentiation of log transformed data
- Generate visit windows visit 1 to visit 8
- Determined the sum of seizures per visit window.
- Log transformed sum of seizures per visit window.

Step 2: Impute missing values assuming MNAR

PROC MI data=<dataset1> nimpute=1 seed=2023 out=<dataset2>;
CLASS treatment sex race ;
MONOTONE regpmm (/details k=5);
MNAR model (visit1-visit8/ modelobs=CCMV(k=8));
VAR treatment fenfluramine_strata weight_strata sex race
age region log(visit1) – log(visit8); **BY** _imputation_ ;
RUN;

Step 3:

For each imputed dataset;

- Exponentiation of log transformed data
- Derived the Baseline and Treatment Period seizure frequency per 28 days
- Derived percent change from baseline
- Rank baseline period seizure frequency per 28 days
- Rank percent change change from baseline in seizure frequency per 28 days

PERFORMING ANALYSIS FOR EACH IMPUTED DATASET:

PROC MIXED data=<dataset2>;
CLASS treatment(ref='placebo') fenfluramine_strata weight_strata ;
MODEL rank_value=baseline_rank treatment fenfluramine_strata weight_strata region;
LSMEANS treatment/diff;
BY _imputation_;
ODS OUTPUT Diffs=<dataset3>;
RUN;

COMBINE RESULTS:

PROC MIANALYZE data=<dataset3>;
MODELEFFECTS estimate;
STDERR stderr;
ODS OUPUT PARAMETERESTIMATES= <dataset4>;
RUN;

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS v 9.4 or later.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2020 Dec 21;394(10216):2243–54.

Rubin, DB. Multiple Imputations for Nonresponse in Surveys. New York: John Wiley & Sons; 1987.

Pocock, SJ, Simon, R. Sequential Treatment Assignment with Balancing for Prognostic Factors in the Controlled Clinical Trial. Biometrics. Mar 1975 Vol 31: 103-115.

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 1,

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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
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
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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
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
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 cel

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