16.1.1 Protocol and Protocol Amendments

The latest version of the study protocol and previous version are provided on the following pages:

- V2.0 Final, 17 Jun 2018 (per Amendment 01)
- V1.0 Final, 30 May 2018 (original protocol)

REVISION HISTORY

Revisions to Version 1.0 **Amended version/Date: FINAL: v2.0, 17 June 2018 (per Administrative Change 01)**		
Change	**Rationale**	**Affected Protocol Sections**
Clarified that a light snack can be provided at 30 minutes predose (after clinical laboratory blood collection) and at 2 hours postdose)	Document quality	Synopsis – Study Design
Clarification of timing of full and brief neurological examinations during the study.	Document quality and clarity	Table 5, footnote b
Correction of footnote for IPS procedure	Document quality	Table 5

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2730-A001-201
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Cross-Over Study Evaluating Pharmacodynamic Activity of E2730 in Adult Subjects with Photosensitive Epilepsy
Sponsor:	Eisai Inc. 100 Tice Boulevard, Woodcliff Lake, New Jersey 07677, US
Investigational Product Name:	E2730
Indication:	Not applicable
Phase:	2
Approval Date:	V2.0 17 June 2018 (revised original protocol) V1.0 30 May 2018 (original protocol)
IND Number:	124728
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.: E2730

Name of Active Ingredient: CCI [redacted]

Study Protocol Title

A Multicenter, Double-Blind, Randomized, Cross-Over Study Evaluating Pharmacodynamic Activity of E2730 in Adult Subjects with Photosensitive Epilepsy

Principal Investigator

PPD

Sites

Approximately 6 sites in the US

Study Period and Phase of Development

The total study duration from first subject enrolled to last subject's last visit/last assessment will be approximately 4 to 5 months.

Phase 2

Objectives

Primary Objective

- To assess the pharmacodynamic (PD) activity of E2730 as measured by suppression of epileptic photoparoxysmal response (PPR) in the subject's most sensitive eye condition as a proof of principle of efficacy in subjects with photosensitive epilepsy

Secondary Objectives

- To assess the PD activity of E2730 as measured by suppression of epileptic PPR, onset, maximum change, and duration of response in 3 eye-conditions (eye closure, eyes closed, and eyes open) in subjects with photosensitive epilepsy.
- To assess the safety and tolerability of E2730 following a single oral dose in subjects with photosensitive epilepsy
- To assess the pharmacokinetics (PK) of E2730 following a single oral dose in subjects with photosensitive epilepsy
- To evaluate potential exposure-PD response relationships

CCI [redacted]

- CCI [redacted]

Study Design

This is a multicenter, double-blind, randomized, 6-sequence, 3-treatment, 3-period cross-over study in adult subjects with epilepsy. This study will use the photosensitivity proof of principle model to determine the potential of E2730 to reduce the photosensitive range in adult subjects. This study will have 2 phases: Prerandomization and Randomization. The Prerandomization Phase will consist of a Screening Period (up to 3 weeks), during which each subject's study eligibility will be determined

and baseline assessments will be conducted. The Randomization Phase will consist of 3 Treatment Periods with a single dose in each period (placebo, E2730 40 mg, or E2730 120 mg, each separated by a 3-week (±3 days) washout interval for a total of approximately 6 weeks), and a Follow-up Period (a single visit, 3 weeks ±3 days after the last day of study product administration). All visits will be conducted on an outpatient basis.

At the Screening Visit (Visit 1), subjects will undergo an electroencephalogram intermittent photic stimulation (EEG-IPS) assessment in 3 eye-conditions (eye closure, eyes closed, and eyes open) at ascending and then descending photo-stimulation frequencies. The Screening Visit EEG-IPS assessment will be performed at 5 time points, over an approximately 4-hour time period (0, 1, 2, 3, and 4 hours; within ±15 minutes of the scheduled time point). Subjects with a reproducible PPR on EEG of at least 3 points on the standardized photosensitivity response (SPR) scale in at least 1 eye condition on at least 3 of the EEGs performed at Screening will be eligible for the study. The baseline assessments will be conducted, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency for each eye condition. Qualified medical personnel for the management of acute seizures will be present during the day of EEG-IPS procedure throughout the duration of the study.

Within 21 days of the Screening Visit (Visit 1), subjects will be asked to return to the study site for Visit 2 (Day 1), when the final determination of eligibility will be made. Subjects will be randomized, enter the Randomization Phase, and will begin Treatment Period 1.

Subjects meeting eligibility criteria will be randomized into 1 of 6 treatment sequences to receive, in a blinded fashion, a single oral dose of placebo control, E2730 40 mg, or E2730 120 mg and begin the Randomization Phase. On the day of each Treatment Visit (ie, Day 1, Day 22, Day 43), subjects will arrive at the clinic in the morning following an overnight fast of at least 8 hours, and the baseline assessments will be conducted again at predose, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency for each eye condition. Study drug product will be administered with approximately 240 mL (8 fluid ounces) of water. Additional water may be provided in increments of 50 mL (up to a maximum of 100 mL), if required. A light snack can be provided at at 30 minites pre-dose (after clinical laboratory blood collection) and 2 hours postdose (revised per Administrative Change 01). Water will be permitted ad libitum except from the time of dosing until 1 hour postdose. Each treatment period will be separated by a 3-week (±3 days) washout interval.

The safety, tolerability, and PK of E2730 will be assessed. A full neurological examination and vital signs evaluation will be performed at screening and a brief neurological examination will be performed at predose and at scheduled time points after dosing. E2730 activity will be characterized by EEG-IPS, for a minimum of 2.5 minutes under all eye conditions (eye closure, eyes open, and eyes closed) on each treatment day. EEG-IPS sessions will be assessed on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4) at 30 minutes to 2 hours predose and 1, 2, 4, 6, and 8 hours postdose time points. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered at screening, postdose at the end of every treatment visit, and at the Follow-up/Early discontinuation visit. Bond and Lader scale for central nervous system (CNS)–related sedative adverse effects will be measured for each subject at predose, 1, 2, 4, 6, and 8 hours postdose at every visit. There will be an interval of 21±3 days between scheduled subsequent visits between dosing days.

After completing Treatment Period 3, all subjects will enter the Follow-up period during which they will be required to complete a Follow-up visit at 3 weeks ±3 days following the last day of study product administration. The end of study is defined as the last subject completing the Follow-up Visit. The anticipated study participation duration for each subject is approximately 12 weeks.

Early Discontinuation

Subjects who discontinue study drug before completing all treatments in the study, for any reason,

will undergo an Early Discontinuation (ED) Visit within 3 weeks ±3 days of their last dose of study drug.

Number of Subjects

Approximately 9 subjects will be randomized to achieve 6 evaluable subjects. Subjects who discontinue from the study early may be replaced, after consultation with the sponsor.

Inclusion Criteria

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

1. Male or female 18 to 60 years of age at the time of informed consent.
2. A diagnosis and history of a PPR on EEG with or without a diagnosis of epilepsy.
3. Currently taking up to a maximum of 3 concomitant antiepileptic drugs (AEDs). If taking concomitant AED(s), the dose must have remained stable for at least 4 weeks prior to screening.
4. A reproducible IPS-induced PPR on EEG of at least 3 points on a frequency assessment scale (SPR) in at least 1 eye condition on at least 3 of the EEGs performed at Screening.
5. A body mass index (BMI) between 18 to 35 kg/m^2 and a total body weight greater than or equal to 45 kg at the time of Screening.
6. Agrees to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period prior to each treatment day.
7. Willing and able to comply with all aspects of the protocol.

Exclusion Criteria

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

0. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] *(*or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). 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.

1. Females of childbearing potential who:

Within 30 days before study entry, have had unprotected sexual intercourse and did not use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or 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. If currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 28 days after study drug discontinuation. Females who are using hormonal contraceptives must be on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 28 days after study drug discontinuation.

NOTE: All 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).

2. Male subjects who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.
3. History of nonepileptic seizures (eg, metabolic, structural, or pseudoseizures) while on any antiepileptic medication(s).
4. History of status epilepticus while on any antiepileptic medication(s) within 2 years prior to Screening.
5. Ongoing or history of generalized tonic-clonic seizures within 6 months prior to Screening.
6. Previously developed or who experienced a clinical seizure during prior PPR assessment or screening IPS procedure, respectively.
7. CCI [redacted]
8. Multiple drug allergies or a severe drug reaction to AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
9. Current evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) with the exception of epilepsy, which in the opinion of the investigator could affect the subject's safety or interfere with the study assessments.
10. An active CNS infection, demyelinating disease, degenerative neurological disease or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results.
11. Current evidence of clinically significant active liver disease, porphyria, or with a family history of severe hepatic dysfunction indicated by abnormal liver function tests greater than 3 times the upper limit of normal (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).
12. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening.
13. Known to be human immunodeficiency virus (HIV) positive.
14. History of drug or alcohol dependency or abuse within the 12 months before Screening, or those who have a positive drug test or alcohol test at Screening.
15. Concomitant use of cannabinoids.
16. Inability to follow restriction on watching television, or use of any device with an animated screen (ie, computer, video games, tablets) 24 hours before dosing.
17. A history of prolonged QT syndrome or risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome), or the use of concomitant medications that prolonged the QT/corrected QT (QTc) interval; or prolonged QT/QTc interval (QTc >450 msec) demonstrated on ECG at Screening or Baseline (based on average of triplicate ECGs).
18. Any suicidal ideation with intent with or without a plan within 6 months before Screening or during Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS).

19. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS).
20. Any psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years.
21. Currently enrolled in another clinical study or used any investigational drug or device within 30 days or 5 half-lives, whichever is longer, preceding informed consent, except the investigational study for the evaluation of commercial IPS machine.
22. Frequent spontaneous background burst or current evidence of proconvulsive activity on EEG (eg, increase in spike-wave activity) at Screening.

Study Treatments

Test Drug: E2730

E2730 will be supplied as active pharmaceutical ingredient in capsule at dose strengths of 40 mg and 80 mg.

Comparator Drug: E2730-matched placebo

Each subject will receive a single oral dose of E2730 40 mg, E2730 120 mg, and matched-placebo in a cross-over sequence according to his/her randomization code.

E2730 40 mg: 1 E2730 40 mg capsule and 1 E2730-matched placebo capsule

E2730 120 mg: 1 E2730 80 mg capsule and 1 E2730 40 mg capsule

Placebo: 2 E2730-matched placebo capsules

Duration of Treatment

Single dose (ie, the Randomization Phase will consist of 3 Treatment Periods with a single dose in each period)

Concomitant Drug/Therapy

Up to 3 concomitant AEDs are allowed during the course of the study, provided that the dosage of concomitant AED(s) has remained stable for at least 4 weeks prior to Screening. During the study, changes to concomitant AEDs (including dosage) are not permitted.

Assessments

Efficacy Assessments

Not applicable

Pharmacokinetic Assessments

Blood samples for the determination of E2730 plasma concentrations and its *N*-acetyl metabolite (M1) will be collected at predose and postdose at 1, 2, 4, 6, and 8 hours on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4). In case of early discontinuation, a PK sample will be taken.

Pharmacodynamic Assessments

PD activity of E2730 will be assessed by suppression of PPR following IPS under 3 conditions (eye closure, eyes closed, and eyes open) using the Grass PS 33 photic stimulator with an unpatterned glass lamp and an intensity of 100cd/m^2/flash at 30 minutes to 2 hours predose, and at 1, 2, 4, 6, and 8 hours postdose. The time course (30 minutes to 2 hours predose to 8 hours postdose) will help assess the onset, maximum change, and duration of the reduction in PPR response. PPR is expected to be within the range from 2 Hz to 60 Hz, depending on subject sensitivity to IPS.

The Bond and Lader Visual Analogue Scale (VAS) for CNS–related sedation effects will be measured for each subject at predose, 1, 2, 4, 6, and 8 hours postdose on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4).

All PD assessments will be performed within ±15 minutes of the scheduled time point.

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Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs); laboratory evaluation for hematology, blood chemistry, and urine values; measurement of vital signs and ECGs; and the performance of neurological and physical examinations.

An assessment of suicidality using the C-SSRS will be performed at Screening, during each Treatment visit (postdose), and at the Follow-up/ED Visit.

Other Assessments

Not applicable

Bioanalytical Methods

Plasma concentrations of E2730 and the *N*-acetyl metabolite (M1) will be measured using validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods.

Statistical Methods

Descriptive statistics will be presented including mean and standard deviation of photosensitivity range for each subject at Screening and at each time point, for each Treatment visit day by treatment group. Graphical displays of the data for each subject will allow exploration of intersubject and intrasubject variability.

Details of statistical methods and analyses will be specified in the statistical analysis plan (SAP).

Study Endpoints

Primary Endpoint

Mean change from baseline in the PPR range in each subject's most sensitive eye condition at each dose level of E2730 as compared to placebo

Secondary Endpoints

- Mean changes from baseline in PPR ranges in each subject's eye closure, eyes closed, and eyes open condition at each dose level of E2730 as compared to placebo
- Onset, maximum change, and duration of photosensitivity response at each dose level in all 3 eye conditions at the time course of E2730 as compared to placebo
- Frequency and percentage of subjects with Complete Suppression, Partial Response, and no Response of PPR at each dose level of E2730 as compared to placebo
- Occurrence of AEs or changes in the neurological examination after single doses of E2730 compared to placebo
- Changes in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2730 compared to placebo
- PK of E2730 and its *N*-acetyl metabolite, M1
- Relationship between PK parameters of E2730 onset, maximum change, and duration of impact on photosensitivity

Analysis Sets

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

The Pharmacokinetic Analysis Set is the group of randomized subjects who receive at least 1 dose of

study drug and have sufficient PK data to derive at least 1 PK parameter.

The Pharmacodynamic Analysis Set is the group of randomized subjects who receive at least 1 dose of study drug and have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

Not Applicable

Pharmacokinetic, Pharmacodynamic, CCI [redacted] Analyses

Pharmacokinetic Analyses

The PK Analysis Set will be used for listings of individual E2730 and *N*-acetyl metabolite (M1) plasma concentrations, summaries and listings of PK parameters. Plasma concentrations will be tabulated by nominal sampling time and summarized by treatment dose using summary statistics.

The following PK parameters will be derived by noncompartmental analysis using plasma concentrations of E2730 and M1. These parameters will include, but are not limited to:

C_{max} maximum observed concentration

$AUC_{(0\text{-}8h)}$ area under concentration x time curve from time 0 to 8 hours postdose

t_{max} time to reach C_{max} following drug administration

The PK of E2730 will be analyzed based on available data from this study. The PK and PD Analysis datasets will be used to evaluate the relationship of PK of E2730 and change in PPR response. The PK-PD analyses may include the examination of the relationship of PK of E2730 and PPR response (eg, time of onset, maximum change, and duration of PPR; Bond and Lader data) using model-based approaches.

Pharmacodynamic Analyses

The PD analysis will be performed on the PD Analysis Set.

No multiplicity adjustments will be made. The 5 PPR measured postdose on a study day will be averaged and used for the primary endpoint. The predose PPR data from the respective treatment period will be used as the baseline data.

The primary and secondary endpoints of mean change from baseline of the average PPR for each E2730 dose compared with placebo in the most sensitive and different eye conditions will be performed using a mixed effects model for crossover study. The model will include treatment, period, and sequence as fixed effects, baseline (predose) measurement as a covariate, and subject nested within sequence as a random effect. Where data are normally distributed, least squares (LS) means, difference in LS means of each E2730 dose compared to placebo, and 90% CIs will be presented with no adjustments for multiplicity.

Additional analysis by graphical exploration on onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions at the time course of E2730 as compared to placebo. This analysis will provide further information on the frequency and percentage of subjects with Complete Suppression, Partial Response, and No Response of PPR at each dose level of E2730 as compared to placebo.

Sensitivity analyses for PPR may be conducted, for example, of PPR for subjects who completed Treatment Periods 1-3 versus those who are included in the PD Analysis Set. CCI [redacted]

All PD data (Bond and Lader) will be listed and summarized by treatment, as appropriate, using standard summary statistics. Descriptive summary statistics (eg, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent for categorical variables) of each endpoint and the changes from baseline will be tabulated.

CCI [redacted]

CCI [redacted]

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and neurological/physical examinations. Treatment-emergent adverse events (TEAEs) will be summarized by presenting for each treatment group, the incidence of AEs. An assessment of suicidal ideation and behavior using the C-SSRS will be performed throughout the study.

Descriptive summary statistics (eg, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent for categorical variables) of the laboratory, vital signs, ECG parameters, and changes from baseline will be evaluated by treatment group. The proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors will be summarized.

Interim Analyses

No formal interim analysis is planned.

Sample Size Rationale

Approximately 9 subjects with photosensitive epilepsy and a stable PPR will be needed to be randomized in the study in order to obtain 6 evaluable subjects. Based on a similar study in subjects with photosensitive epilepsy (NCT02564029), an estimated standard deviation of the treatment group difference of the SPR in the subject's most sensitive eye condition is 3.62. The width of a 90% CI of the mean group difference based on this standard deviation assumption and 6 subjects is 2.431. Therefore, a sample size of 6 would be sufficient to detect a mean group difference of 3 or larger with 90% confidence.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{(0-24)}$	area under the concentration-time curve from 0 time to fixed time 24 hours
$AUC_{(0-inf)}$	area under the concentration-time curve from 0 time extrapolated to infinity time
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variance
ED	Early Discontinuation (Visit)
EEG-IPS	electroencephalogram intermittent photic stimulation
CCI	[redacted]
GM	geometric mean
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPS	intermittent photic stimulation
IRB	Institutional Review Board
LNH	low/normal/high
LS	least squares
M1	E2730 N-acetyl metabolite
MedDRA	Medical Dictionary for Regulatory Activities
Max	maximum
Min	minimum
n/a	not applicable

Abbreviation	Term
PD	pharmacodynamic
CCI	[redacted]
PI	principal investigator
PK	pharmacokinetics
POC	proof-of-concept
PPR	photoparoxysmal response
PT	preferred term
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAD	single ascending dose
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
SPR	standardized photosensitivity response
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
$t_{1/2}$	terminal elimination phase half-life
t_{max}	time at which the highest drug concentration occurs
VAS	Visual Analogue Scale

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), 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 (Code of Federal Regulations [CFR], Title 21 CFR Parts 50 and 56). Any protocol amendment or revision to the ICF 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.

A signed letter of study approval from the IRB chairman must be sent to the principal investigator (PI) 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 the 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 will forward a copy to the sponsor at the time of each periodic report. The investigator 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.

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 and Competent Authority within 15 calendar days, 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 (SOP) 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
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use

- Title 21 of the United States Code of Federal Regulations (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 document, the investigator must explain to each subject 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, and the extent of maintaining confidentiality of the subject's records. Each subject 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 treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject 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, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject 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 will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. CCI [redacted]

An unsigned copy of an IRB-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject 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 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 6 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 organizations (CROs) will be provided to each site.

7 INTRODUCTION

7.1 Indication

The initial goal is to develop E2730 as an antiepileptic drug (AED) in patients with a rare form of epilepsy, in parallel with partial-onset seizure studies in adolescents and adults. The selection of the disease candidate for orphan drug treatment will be based on ongoing and planned preclinical studies in house and at external institutions.

7.1.1 Mechanism of Action – E2730

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7.1.2 Clinical Experience With E2730

The E2730 clinical program to date comprises 1 completed Phase 1 study in which 6 healthy subjects received single doses of E2730 (20 mg) and 2 healthy subjects received placebo. The first-in-human single ascending dose (SAD) study of E2730 (E2730-A001-001; Study 001), was initially planned to administer E2730 with dose escalation conducted in sequential dose groups consisting of 8 subjects per group randomized (3:1) to receive single ascending E2730 doses of 20, 40, or 80 mg or E2730-matched placebo. Dose escalation could only occur if the available data supported an increase in dose that did not exceed plasma E2730 exposures predefined for Cmax=1.5 µg/mL or area under the concentration-time curve from zero time extrapolated to infinite time (AUC(0-inf))=20µg•h/mL. This threshold was originally required by the Food and Drug Administration (FDA) and was reached with the first E2730 dose (20 mg). Thus, no higher E2730 doses were administered.

The SAD study (E2730-A001-002; Study 002) is currently ongoing, where doses of 40, 80, 120, and 160 mg are planned in healthy subjects. The proposed doses are anticipated not to exceed 3 μg/mL, per the FDA's revised limit on the Cmax, and the data will be evaluated on an ongoing basis during each dose escalation. The anticipated Cmax of the highest dose cohort (120 mg cohort) in the current study is likely not to exceed the prespecified threshold.

7.1.2.1 Pharmacokinetics

In Study 001 and Study 002, which enrolled healthy subjects (18-50 years); E2730 was rapidly absorbed after a single oral administration of 20, 40, 80, and 120 mg. Plasma E2730 concentrations peaked at 1.25 to 5.5 hours. The *N*-acetyl metabolite (M1) was sparsely detected just above or at the lower limit of quantification, thus a complete plasma M1 pharmacokinetic (PK) profile could not be derived. Pharmacokinetic parameters in Study 001 and Study 002 are shown in Table 1. Although C_{max} and $AUC_{(0-24)}$ were less than dose proportional between 20 mg and 40 mg, there was almost dose proportional from 40 mg through 120 mg. The highest individual C_{max} value (2.930 μg/mL) of 120 mg was not to exceed the prespecified threshold of 3 μg/mL. There was 1 subject who had low plasma E2730 concentration (C_{max}: 0.222 μg/mL) in the 120 mg cohort. The plasma E2730 concentration declined with a mean terminal elimination phase half-life ($t_{1/2}$) of 59.0 to 69.8 hours.

Table 1 PK Parameters In Study 001 (20 mg) and Study 002 (40 mg, 80 mg, and 120 mg)

Dose	t_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng•h/mL)	$AUC_{(0-inf)}$ (ng•h/mL)	$t_{½}$ (h)
20 mg	1.25 (0.50, 1.50)	351 (22.7)	6330 (23.9)	28600 (11.5)	69.8 (21.9)
40 mg	3.00 (1.50, 6.00)	496 (20.3)	9210 (19.6)	41300 (15.9)	69.7 (15.2)
80 mg	5.50 (1.00, 8.00)	899 (14)	16900 (12.7)	61100 (6.44)	59.0 (15.8)
120 mg	4.50 (0.50, 8.00)	1270 (116)	23300 (110)	n/a[a]	n/a[a]

$AUC_{(0-24)}$ = area under the concentration-time curve from 0 time to fixed time 24 hours; $AUC_{(0-inf)}$ = area under the concentration-time curve from 0 time extrapolated to infinity time; PK = pharmacokinetics, max = maximum; min = minimum; $t_{1/2}$ = terminal elimination phase half-life; t_{max} = time at which the highest drug concentration occurs, n/a = not applicable; CV = coefficient of variance.

Note: All PK parameters, except t_{max}, are presented as geometric mean (%CV). t_{max} is presented as median (min, max).

a. As of the data cut-off date of 22 May 2018, plasma concentrations of E2730 at 120 mg are available until 24 hours post dose.

After administration of E2730 20 mg, the GM percent of recovered parent drug in urine collected up to 96 hours postdose was 21.8% and a smaller fraction (GM=0.728%) was excreted as M1.

7.1.2.2 Safety and Tolerability

E2730 was well tolerated in healthy adult subjects when administered as single oral doses across the dose range of 20 to 120 mg (Study 001 and Study 002). The maximum tolerated dose (MTD) has not yet been reached (Study 002).

Among 6 subjects who received 20 mg E2730 (Study 001), 1 subject experienced a TEAE (postural orthostatic tachycardia syndrome) on the day of administration. The event was mild in severity and resolved on the same day without treatment. The investigator judged the event to be related to the study drug. Another subject experienced a TEAE (dizziness) on the day of placebo administration. The event was mild in severity and resolved on the same day without treatment. The investigator judged the event to be related to the study drug.

From the blinded preliminary safety results in 40 mg and 80 mg, 4 subjects experienced 6 TEAEs (sleepiness, insomnia, nausea, drowsiness [2 subjects], and decrease appetite) and 4 subjects experienced 8 TEAEs (orthostatic tachycardia [2 subjects], dermatitis contact, atrioventricular block, dizziness, headache, insomnia, and diarrhea), respectively. There were no medically significant findings from vital signs in 40 mg and 80 mg cohorts.

In the 120 mg cohort, the safety data have been reviewed through Day 13. Clinically significant findings in vital signs were reported for 2 subjects, which were characterized as AEs of orthostatic tachycardia and hypotension. Both AEs were mild and in both cases, subjects were asymptomatic. There were no deaths or SAEs, and no medically significant findings have been reported from EEG or ECG (no significant QT or QTc prolongations). There have been no clinically significant laboratory abnormalities. There were no epileptiform discharges or clinically significant abnormalities of EEG observed in the 40 mg, 80 mg, or 120 mg dose cohorts.

7.2 Study Rationale

7.2.1 Photosensitivity Proof of Concept Model

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8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to assess the PD activity of E2730 as measured by suppression of epileptic PPR in the subject's most sensitive eye condition as a proof of principle of efficacy in subjects with photosensitive epilepsy.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the PD activity of E2730 as measured by suppression of epileptic PPR, onset, maximum change, and duration of response in 3 eye-conditions (eye closure, eyes closed, and eyes open) in subjects with photosensitive epilepsy.

- To assess the safety and tolerability of E2730 following a single oral dose in subjects with photosensitive epilepsy.
- To assess the PK of E2730 following a single oral dose in subjects with photosensitive epilepsy.
- To evaluate potential exposure-PD response relationships.

8.3 CCI

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9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, double-blind, randomized, 6-sequence, 3-treatment, 3-period cross-over study in adult subjects with epilepsy. This study will use the photosensitivity proof of principle model to determine the potential of E2730 to reduce the photosensitive range in adult subjects. This study will have 2 phases: Prerandomization and Randomization. The Prerandomization Phase will consist of a Screening Period (up to 3 weeks), during which each subject's study eligibility will be determined and baseline assessments will be conducted. The Randomization Phase will consist of 3 Treatment Periods with a single dose in each period (placebo, E2730 40 mg, or E2730 120 mg, each separated by a 3-week (±3 days) washout interval for a total of approximately 6 weeks), and a Follow-up Period (a single visit, 3 weeks ±3 days after the last day of study product administration). All visits will be conducted on an outpatient basis.

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

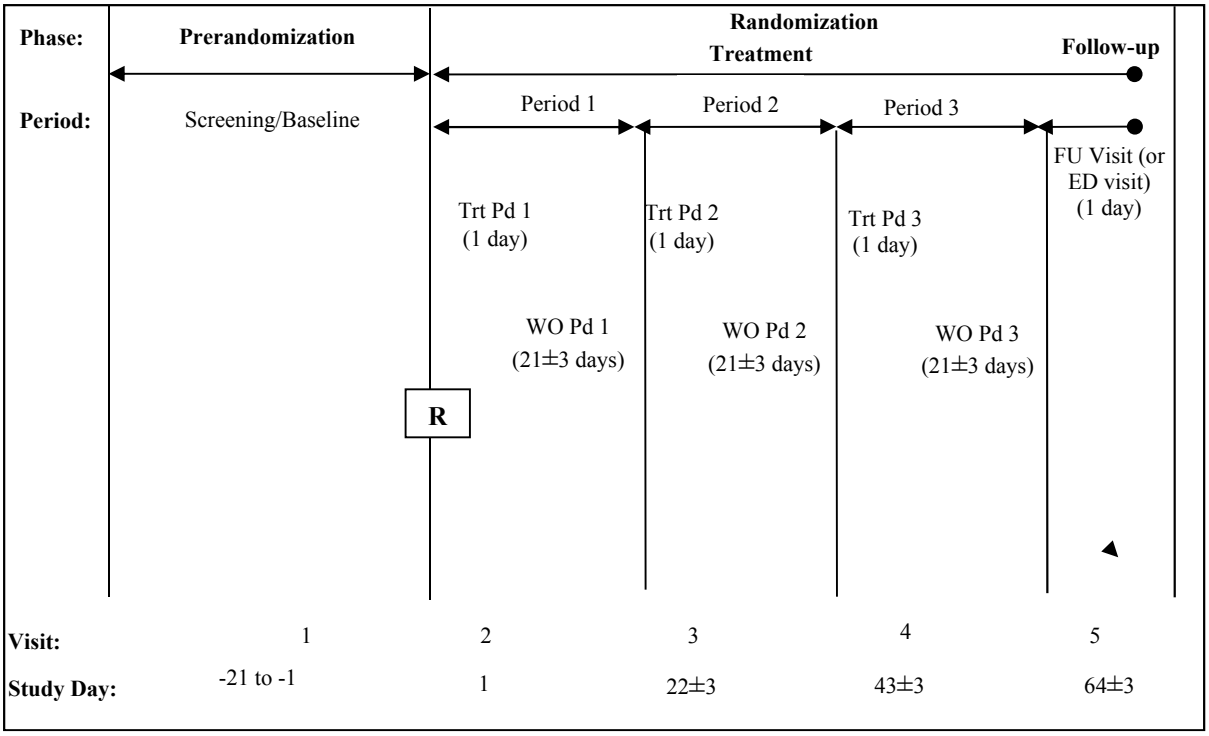

Figure 1 Study Design for a Crossover Study

ED = Early discontinuation, FU = Follow Up, Pd = period, R = randomization, Trt = treatment, WO = washout

9.1.1 Prerandomization Phase

The Prerandomization Phase will consist of a Screening Period (up to 3 weeks), during which each subject's study eligibility will be determined and baseline assessments will be conducted.

9.1.1.1 Screening Period

Screening will occur between Day –21 and Day –1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis and history of a PPR on EEG with or without a diagnosis of epilepsy for which they are receiving up to 3 concomitant AEDs.

The Screening Disposition case report form (CRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

At the Screening Visit (Visit 1), subjects will undergo an EEG-IPS assessment in 3 eye-conditions (eye closure, eyes closed, and eyes open) at ascending and then descending photo-stimulation frequencies. The Screening Visit EEG-IPS assessment will be performed at 5 time points, over an approximately 4-hour time period (0, 1, 2, 3, and 4 hours; within ±15 minutes of the scheduled time point). Subjects with a reproducible PPR on EEG of at least 3 points on the SPR scale in at least 1 eye condition on at least 3 of the EEGs performed at Screening will be eligible for the study. The baseline assessments will be conducted, including determination of the lower and upper limit of photosensitivity to intermittent photic stimulation (EEG-IPS) threshold frequency for each eye condition. Qualified medical personnel for the management of acute seizures will be present during the day of EEG-IPS procedure throughout the duration of the study.

9.1.2 Randomization Phase

The duration of the Randomization Phase will be 9 weeks and will include 3 Treatment Periods (placebo, E2730 40 mg or E2730 120 mg, each separated by a 3-week (±3 days) washout interval, for a total of approximately 6 weeks), and a Follow-up Period (a single visit, 3 weeks ±3 days after the last day of study product administration). Subjects whose screening assessments and evaluations (including Day 1 [Visit 2] procedures) are completed and reviewed by the investigator and who continue to meet all of the inclusion/exclusion criteria will enter the Randomization Phase. The baseline assessments will be conducted again at predose of each Treatment Period, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency for each eye condition.

9.1.2.1 Treatment Periods

Subjects will be randomized into 1 of 6 treatment sequences to receive placebo, E2730 40 mg, or E2730 120 mg. Each of the 3 treatment periods will be separated by a 3-week (±3 days) washout interval.

9.1.2.2 Follow-up Period

After completing Treatment Period 3, all subjects will enter the Follow-up period during which they will be required to complete a Follow-up visit. The Follow-up Period is a single visit, 3 weeks ±3 days after the last day of study product administration.

9.2 Discussion of Study Design, Including Choice of Control Groups

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 9 subjects will be randomized to achieve 6 evaluable subjects at approximately 6 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 18 to 60 years old at the time of informed consent.
2. A diagnosis and history of a PPR on EEG with or without a diagnosis of epilepsy.
3. Currently taking up to a maximum of 3 concomitant antiepileptic drugs (AEDs). If taking concomitant AED(s), the dose must have remained stable for at least 4 weeks prior to screening.
4. A reproducible IPS-induced PPR on EEG of at least 3 points on a frequency assessment scale (SPR) in at least 1 eye condition on at least 3 of the EEGs performed at Screening.
5. A body mass index (BMI) between 18 to 35 kg/m^2 and a total body weight greater than or equal to 45 kg at the time of Screening.
6. Agrees to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period prior to each treatment day.
7. Willing and able to comply with all aspects of the protocol.

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 [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). 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:
   a) Within 30 days before study entry, have had unprotected sexual intercourse and did not use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia)
   b) 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. If

currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 28 days after study drug discontinuation. Females who are using hormonal contraceptives must be on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 28 days after study drug discontinuation.

NOTE: All 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. Male subjects who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.
4. History of nonepileptic seizures (eg, metabolic, structural, or pseudoseizures) while on any antiepileptic medication(s).
5. History of status epilepticus while on any antiepileptic medication(s) within 2 years prior to Screening.
6. Ongoing or history of generalized tonic-clonic seizures within 6 months prior to Screening.
7. Previously developed or who experienced a clinical seizure during prior PPR assessment or screening IPS procedure, respectively.
8. CCI [redacted]
9. Multiple drug allergies or a severe drug reaction to AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
10. Current evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) with the exception of epilepsy, which in the opinion of the investigator could affect the subject's safety or interfere with the study assessments.
11. An active central nervous system (CNS) infection, demyelinating disease, degenerative neurological disease or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results.
12. Current evidence of clinically significant active liver disease, porphyria, or with a family history of severe hepatic dysfunction indicated by abnormal liver function tests greater than 3 times the upper limit of normal (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).
13. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening.
14. Known to be human immunodeficiency virus (HIV) positive.
15. History of drug or alcohol dependency or abuse within the 12 months before Screening, or those who have a positive drug test or alcohol test at Screening.

16. Concomitant use of cannabinoids.
17. Inability to follow restriction on watching television, or use of any device with an animated screen (ie, computer, video games, tablets) 24 hours before dosing.
18. A history of prolonged QT syndrome or risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome), or the use of concomitant medications that prolonged the QT/corrected QT (QTc) interval; or prolonged QT/QTc interval (QTc >450 msec) demonstrated on ECG at Screening or Baseline (based on average of triplicate ECGs).
19. Any suicidal ideation with intent with or without a plan within 6 months before Screening or during Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS).
20. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS).
21. Any psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years.
22. Currently enrolled in another clinical study or used any investigational drug or device within 30 days or 5 half-lives, whichever is longer, preceding informed consent, except the investigational study for the evaluation of commercial IPS machine.
23. Frequent spontaneous background burst or current evidence of proconvulsive activity on EEG (eg, increase in spike-wave activity) at Screening.

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.

9.3.3.1 Study-Specific Withdrawal Criteria

The investigator will determine continued subject participation in the IPS assessments. In individual situations, safety assessments will be completed as appropriate, determined by the investigator.

A subject may be withdrawn from the study if any of the following circumstances occur:

1. If a subject experiences a generalized tonic-clonic seizure on any study day, and the subject has not had a generalized tonic-clonic seizure in the 6 months prior to enrollment, that subject will be discontinued from the study.

OR

1. If a subject experiences a generalized tonic-clonic seizure during IPS, that subject will be discontinued from the study.
2. If, in the opinion of the investigator, a subject has evidence of proconvulsive activity on the EEG (eg, increase in spike-wave activity), following administration of the study drug.

3. If a subject has widening of the photosensitivity range by more than 3 points on 2 consecutive occasions after dosing as compared to Screening, the IPS will be terminated and the subject will not be permitted to participate in further testing on the same day.

Generalized spike and wave discharges greater than 5 seconds defined by absence seizures or isolated myoclonic jerks do not require stoppage of study drug or subject withdrawal.

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

E2730 is the test drug and will be supplied as active pharmaceutical ingredient in capsule at dose strengths of 40 mg and 80 mg. Study site personnel will administer capsules containing E2730 or matched placebo (Table 2) as single oral doses according to the study design. Filled capsules will be packed, labelled, and shipped by the contract manufacturer to each site.

Each subject will receive a single oral dose in a cross-over sequence according to his/her randomization code (Table 3). The following treatments will be administered as a single dose to subjects.

- E2730 40 mg: 1 E2730 40 mg capsule and 1 E2730-matched placebo capsule
- E2730 120 mg: 1 E2730 80 mg capsule and 1 E2730 40 mg capsule
- Placebo: 2 E2730-matched placebo capsules

Table 2 Treatments Administered

Treatment	Study Drug Administered
A	Placebo
B	E2730 40 mg
C	E2730 120 mg

Table 3 Treatment Sequences

Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3
1: ABC	Placebo	E2730 40 mg	E2730 120 mg
2: BCA	E2730 40 mg	E2730 120 mg	Placebo
3: CAB	E2730 120 mg	Placebo	E2730 40 mg
4: ACB	Placebo	E2730 120 mg	E2730 40 mg
5: BAC	E2730 40 mg	Placebo	E2730 120 mg
6: CBA	E2730 120 mg	E2730 40 mg	Placebo

A = Placebo; B = E2730 40 mg; C = E2730 120 mg

9.4.2 Identity of Investigational Product(s)

E2730 will be supplied in powder form as the free base.

9.4.2.1 Chemical Name, Structural Formula of E2730

- Test drug code: E2730

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9.4.2.2 Comparator Drug

Placebo capsule matched to E2730 capsule will be administered.

9.4.2.3 Labeling for Study Drug

E2730 will be labeled in accordance with text that is in full regulatory compliance.

9.4.2.4 Storage Conditions

E2730 will be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that E2730 is maintained within 2ºC to 8ºC. 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 all 3 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.

9.4.4 Selection of Doses in the Study

E2730 is currently studied in the SAD study (Study 002). In rat amygdala kindling model, which is considered the most clinically relevant animal model for investigating the effect of compound on partial-onset seizures, E2730 showed a significant and dose-dependent antiseizure effect after the single oral administration.

Two doses are currently being considered for this study. Based on the data from the ongoing Study 002, the anticipated exposure at the dose of 120 mg will be within the exposure limits imposed by the FDA. An additional, lower dose of 40 mg is being considered to provide exposure data to further evaluate PK/PD relationship of E2730. The data from this study will also support initial dose response analysis and provide a dose for future studies.

The doses in this study will be finalized after all cohorts in Study 002 have been evaluated.

9.4.5 Selection and Timing of Dose for Each Subject

Following an overnight fast of at least 8 hours, subjects will be administered the study drug product with approximately 240 mL (8 fluid ounces) of water on the day of each Treatment Visit (ie, Day 1, Day 22, and Day 43). A light snack can be provided at 30 minutes predose (after clinical laboratory blood collection) and at 2 hours postdose.

9.4.6 Blinding

During the Prerandomization and Randomization Phases, central EEG reading will be performed in a blinded and independent manner. Investigator(s) may consult with the central read only during the Prerandomization Phase, if needed, for EEG-IPS eligibility determination.

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel (with the exception of the pharmacist preparing and dispensing the study drug), and sponsor staff will be blinded to the treatment codes. Randomization code 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.

The E2730 drug substance and placebo will be provided to an unblinded pharmacist in an open-label manner. The unblinded pharmacist will be responsible for preparing and dispensing study drug capsules in accordance with subject randomization in a blinded manner. A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the sponsor. In addition, master code breaker reports or envelopes identifying the treatment group of each subject number will be provided to the site and to the sponsor in sealed envelopes. These code breaker reports or envelopes are not to be opened unless an emergency occurs and knowledge of the subject's randomization code may affect his/her medical treatment. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. The investigator is to record the date and time of opening the code breaker report or envelope and the reason for breaking the code. At the conclusion of the study, where possible, all unused drug supplies at the site, together with master code breaker reports or envelopes, are to be returned to the clinical supply vendor for final reconciliation and disposition.

Data from any completed cohort may be unblinded for review by the sponsor.

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) will be recorded on the Prior & Concomitant Medication CRF or Non-Pharmacological Procedures CRF. Up to 3 concomitant AEDs (Appendix 2) are allowed during the course of the study, provided that the dosage of concomitant AED(s) has remained stable for at least 4 weeks prior to screening. During the study, changes to concomitant AEDs (including dosage) are not permitted.

The investigator will record on the AE CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

9.4.7.1 Prohibited Concomitant Therapies and Drugs

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9.4.7.2 Restrictions During the Study Period

Study drug will be administered on the day of each Treatment Visit (ie, Day 1, Day 22, and Day 43) after an overnight fast of at least 8 hours. Treatments will be administered orally with approximately 240 mL (8 fluid ounces) of water. A light snack can be provided at 30 minutes predose (after clinical laboratory blood collection) and at 2 hours postdose.

Water will be allowed as desired except from the time of dosing until 1 hour after study drug administration.

Subjects will be required to abstain from watching television or using any device with an animated screen (ie, computer, video games, tablets) within the 24 hour period prior to each dosing. Subjects will be required to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period prior to each treatment day.

9.4.8 Treatment Compliance

Not applicable as study drug will be administered in the study site by study personnel and records will be maintained.

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

- 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
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license
- A signed and dated clinical studies agreement

The investigator and the study staff will be responsible for the accountability of all study drugs (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 study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs 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 study drugs 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 (eg, FDA). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and, together with unused study drugs 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 study drugs and containers at the site. Destruction at the site will only occur under circumstances

where regulation or supply type prohibits the return of study drugs 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, study drugs 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, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are 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 site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

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

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History and Epilepsy Medical History

In addition to standard medical history, surgical, and epilepsy history and current medical conditions will be recorded at the Screening Visit. All medical, surgical, and epilepsy history within 10 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.2.2 Height Measurement and BMI computation

Height (cm) will be recorded at the Screening Visit and BMI (kg/m^2) will be computed from height and weight data at screening.

9.5.1.2.3 Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 5). This sample will be tested for common drugs of use/abuse: eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, opioids (as a group), benzodiazepines, barbiturates, and amphetamines.

9.5.1.2.4 Serology

A 6 mL sample of blood will be taken for hepatitis B surface antigen and hepatitis C antibodies at Screening.

9.5.1.3 Efficacy Assessments

Not applicable

9.5.1.4 Pharmacokinetic, Pharmacodynamic, CCI [redacted] Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples for determination of plasma concentrations of E2730 and its metabolite, M1, will be collected from each subject. PK sampling for plasma concentration will be collected at predose and postdose at 1, 2, 4, 6, and 8 hours on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4). In case of early discontinuation, a PK sample will be taken. Plasma concentrations of E2730 and M1 will be measured using validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods.

Information on the PK sample collection, handling, and shipping procedures will be provided to the clinical site either as a stand-alone PK laboratory manual or as part of the (central) Laboratory Manual.

9.5.1.4.2 PHARMACODYNAMIC, CCI [redacted] ASSESSMENTS

All PD assessments will be performed within ±15 minutes of the scheduled time point.

EEG-IPS

PD activity of E2730 will be assessed by suppression of PPR following IPS under 3 conditions (eye closure, eye closed, eye open) using the Grass PS 33 photic stimulator with an unpatterned glass lamp and an intensity of 100cd/m^2/flash at 30 minutes to 2 hours predose, and at 1, 2, 4, 6, and 8 hours postdose. The time course (30 minutes to 2 hours predose to 8 hours postdose) will help assess the onset, maximum change, and duration of the reduction in PPR response. PPR is expected to be within the range, from 2 Hz to 60 Hz, depending on subject sensitivity to IPS.

Standard 19-21-channel EEG equipment will be used for recording including video monitoring and precise recording of duration and frequency of the flashes (sensor or connection with the photostimulator). The international 10-20 system will be used, with 2 additional channels, 1 for eye-movements (to detect changes in eye-condition more easily) and 1 for flash frequencies. A 19-21-channel recording system will be used with a bipolar derivation with emphasis on the parieto-temporal-occipital area (maximum and spreading of EA). The display montage will include T4-T6-O2-O1-T5-T3 and T4-P4-Pz-P3-T3, apart from 2x4 (8) frontal to occipital leads.

The following settings will be used:

- Amplification: 7-10 microV/mm
- High Frequency Filter: 35-70 Hz
- Time constant: 0.3-0.6 sec

- Display speed: 30 mm/sec

Bond and Lader Visual Analogue Scale

The Bond and Lader visual analogue scale (VAS) for CNS–related sedation effects will be measured for each subject at predose, 1, 2, 4, 6, and 8 hours postdose on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4).

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9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; laboratory evaluation for hematology, blood chemistry, and urine values; measurement of vital signs and ECGs; and the performance of neurological and physical examinations as detailed in Table 5.

An assessment of suicidality using the C-SSRS will be performed as detailed in Table 5.

9.5.1.5.1 Adverse Events and Events Associated with Special Situations

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 E2730.

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
- 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 at 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 observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Randomization Phase and for 5× the half-life of E2730 (mean terminal elimination phase half-life following a single administration of 20 mg E2730 was 71.2 hours in Study 001). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. Serious adverse events (SAEs) must be collected through the last visit in the Randomization Phase and for 5× the half-life of E2730 (mean terminal elimination phase half-life following a single administration of 20 mg E2730 was 71.2 hours in Study 001)..

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 AE CRF.

Abnormal ECG (QTc) 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 interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. 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 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 (see Section 9.5.1.5.8 for a description of the C-SSRS).

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 9.5.1.5.2 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.

9.5.1.5.2 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.

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 (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

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 5) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 4 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	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, calcium, 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.

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 9.5.1.5.1 and the CRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the AE CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [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 5) by a validated method. BP and pulse will be measured after the subject has been supine for 10 minutes. Triplicate reading of supine vital signs will be measured at all visits except for Screening. All BP measurements should be performed on the same arm, preferably by the same person.

At Screening and during Visit 2, Visit 3, and Visit 4, after supine measurements are completed, subjects will be asked to stand up for 2 minutes, and BP and pulse will be taken in the standing position.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

At time points when vital signs, ECGs, and blood sampling are performed concurrently, procedures will be performed in the following order: ECGs, vital signs, and then blood sampling. Subjects will rest in the supine position for 10 minutes before and 5 minutes after ECG recordings followed by recording of vital signs in the supine position and in standing position (BP and pulse only), and lastly blood sampling.

9.5.1.5.5 PHYSICAL EXAMINATIONS

Comprehensive and abbreviated physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 5). 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 AE CRF.

Comprehensive Physical Examination

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, skin, and neurological examination. The subject will be queried regarding physical status and subjective symptoms as well. A urogenital examination will only be required in the presence of clinical symptoms related to this region.

Abbreviated Physical Examination

Health status will be assessed by brief evaluation of the head, eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination.

9.5.1.5.6 NEUROLOGICAL EXAMINATIONS

Comprehensive and abbreviated neurological examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 5). Documentation of the neurological 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 neurological examination findings that meet the definition of an AE will be recorded on the AE CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

Electrocardiograms (12-lead) will be obtained as designated in the Schedule of Procedures/Assessments (Table 5).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AE CRF.

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

C-SSRS

An assessment of suicidality using the C-SSRS will be performed at Screening, postdose at the end of every treatment visit, and at the Follow-up/Early discontinuation visit, as designated in the Schedule of Procedures/Assessments (Table 5).

Pregnancy Test

A serum β-hCG or hCG test will be performed for all women of childbearing potential. A 6-mL sample of blood will be taken at designated time points as specified in the Schedule of Procedures/Assessments (Table 5).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 5 presents the schedule of procedures/assessments for the study.

Table 5 Schedule of Procedures/Assessments in Study E2730-A001-201

Phase	Prerandomization	Randomization				
Period	Screening	Treatment Period 1	Treatment Period 2	Treatment Period 3	Follow-up /Early Discontinuation[a]	Unscheduled
Visit	**1**	**2**	**3**	**4**	**5**	
Study Day	**-21 to -1**	**1**	**22±3**	**43±3**	**64±3**	
Procedures/Assessments						
Informed Consent	X					
Demography	X					
Randomization		X				
Inclusion/exclusion criteria	X	X				
Medical history	X					
Epilepsy medical history	X					
Physical examination[b]	X	X			X	
Neurological examination[b]	X	X	X	X	X	
Vital signs[c]	X	X	X	X	X	X
Height and weight[d]	X	X			X	
12-Lead ECG[e]	X	X	X	X	X	X[f]
Clinical laboratory tests[g]	X	X	X	X	X	X
Urine drug test	X					
Urine pregnancy test[h]		X	X	X	X	
Serum β-hCG [or hCG] test[h]	X					
Serology (HCVAb, HBsAg)	X					
PK sampling (plasma)[i]		X	X	X	X	

Table 5 Schedule of Procedures/Assessments in Study E2730-A001-201

Phase	Prerandomization	Randomization				
Period	Screening	Treatment Period 1	Treatment Period 2	Treatment Period 3	Follow-up /Early Discontinuation[a]	Unscheduled
Visit	1	2	3	4	5	
Study Day	-21 to -1	1	22±3	43±3	64±3	
Procedures/Assessments						
CCI		X				
C-SSRS	X	X	X	X	X	
EEG-IPS Assessment[k]	X[l]	X[m]	X[m]	X[m]		
Bond and Lader VAS[k,n]		X	X	X		
Administer study drug		X	X	X		
Prior and concomitant medication(s)	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

ß-hCG = beta-human chorionic gonadotropin *(*or hCG = human chorionic gonadotropin*)*, BP = blood pressure, C-SSRS = Columbia-Suicide Severity Rating Scale, EEG-IPS= electroencephalogram- intermittent photic stimulation, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, CCI
PK = pharmacokinetics, QTc = corrected QT interval, VAS = visual analogue scale.

a: To be completed for all subjects, including those who discontinue the study early.

b: A full physical examination will be carried out at Screening. A brief physical examination may be carried out at other visits, as deemed necessary by the investigator. A full neurological examination will be performed at screening. A brief neurological examination will be performed during each treatment visit (predose and at 4 hours [±30 minutes] postdose), and during the Follow up/Early Discontinuation visit. Clinically significant abnormal findings from the physical or the neurological examinations will be reported as AEs.

c: Vital signs measurements will be taken at screening. In addition, on each dosing day, vital sign (BP, pulse, body temperature, respiratory rate) measurements will be obtained at predose, 1, 2, 4, 6, and 8 hours postdose. Subjects will need to rest for 10 minutes before vital signs are taken in the supine position. Triplicate reading of supine vital signs will be measured at all visits except for Screening. At Screening and during the Treatment periods, after supine measurements are completed, subjects will be asked to stand up for 2 minutes, and BP and pulse will be taken in the standing position. At time points when vital signs, ECGs, and blood sampling are performed concurrently, procedures will be performed in the following order: ECGs, vital signs, and then blood sampling. Subjects will rest in the supine position for 10 minutes before and 5 minutes after ECG recordings followed

Table 5 Schedule of Procedures/Assessments in Study E2730-A001-201

Phase	Prerandomization	Randomization				
Period	Screening	Treatment Period 1	Treatment Period 2	Treatment Period 3	Follow-up /Early Discontinuation[a]	Unscheduled
Visit	1	2	3	4	5	
Study Day	-21 to -1	1	22±3	43±3	64±3	
Procedures/Assessments						

by recording of vital signs in the supine position and in standing position (BP and pulse only), and lastly blood sampling.

d: At Screening, both height and weight will be measured. At all other visits, only weight will be measured.

e: ECG assessments will be performed in the supine position at predose and 4 hours postdose (on each dosing day). If during any visit the QTc was measured as >450 msec, 3 consecutive ECGs separated by 5 – 10 minutes will be performed to confirm the abnormality.

f: During the unscheduled visits, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.

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

h: Female subjects of childbearing potential only.

i: Blood samples for plasma PK will be obtained at predose and postdose at 1, 2, 4, 6, and 8 hours on Days 1, 22, and 43. In case of early discontinuation, a PK sample will be taken.

j: CCI [redacted]

k: All PD assessments will be performed within ±15 minutes of the scheduled time point.

l: EEG-IPS assessment will be performed at 5 time points, over an approximately 4-hour time period (0, 1, 2, 3, and 4 hours).

m: EEG-IPS assessment will be performed 30 minutes to 2 hours predose and repeated at approximately 1, 2, 4, 6, and 8 hours postdose on Days 1, 22, and 43.

n: The Bond and Lader VAS for CNS–related sedation side effects will be measured from each subject at predose, 1, 2, 4, 6, and 8 hours postdose on Days 1, 22, and 43.

Table 6 presents the blood sampling schedule for pharmacokinetic assessments. In case of early discontinuation, a PK sample will be taken.

Table 6 Blood Sampling Schedule for Pharmacokinetic Assessments

Days	Time Relative to the Administration	Acceptable Time Window
Day 1 (Visit 2), Day 22 (Visit 3) (±3 days), Day 43 (Visit 4) (±3 days)	Predose	–2 hours
	1 and 2 hours	±5 minutes
	4, 6, and 8 hours	±15 minutes

9.5.2.2 Description of Procedures/Assessments Schedule

The scheduling of study procedures and assessments is shown in Table 5.

9.5.3 Appropriateness of Measurements

Most of the clinical assessments are standard measurements commonly used in Phase 2 studies of epilepsy. The safety assessments to be performed in this study, including monitoring and recording all AEs; laboratory evaluation for hematology, blood chemistry, and urine values; measurement of vital signs and ECGs; and the performance of neurological and physical examinations, are standard evaluations to ensure subject safety.

In addition to the standard safety measurements, Bond and Lader VAS will be conducted in this study. The Bond and Lader VAS (Bond, 1974) is a sensitive tool to assess CNS side effects (somnolence, body sway, dizziness and sedation etc.). Since CNS related side effects were observed in nonclinical studies of E2730, Bond and Lader VAS is included for assessment of CNS-related sedation effects in this study.

The EEG-IPS procedure during this study will be performed based upon the protocol of Kastelejin et al (Kastelejin-Nolst Trenité, et al, 1996). The combination of lower and upper frequencies gives a total of 3 photosensitivity ranges, 1 per eye condition (eye closure, eyes closed, and eyes open). In order to minimize the risk of inducing a seizure, photic stimulation will not be carried out between the upper and lower thresholds. However, qualified medical personnel for the management of acute seizures will be present during the day of EEG-IPS procedure throughout the duration of the study.

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 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the last visit in the Randomization Phase and for 5× the half-life of E2730 (mean terminal elimination phase half-life following a single administration of 20 mg E2730 was 71.2 hours in Study 001). 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.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

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 IRB of the occurrence of the SAE in writing, if required by his institution. A copy of this communication must be forwarded to the CRO 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 which the estimated date of conception is either before the last visit or within 28 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, an induced abortion, or a spontaneous abortion 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 1 business day 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 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

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 AE 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 is 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 AE CRF.

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

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. 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 ED procedures indicated in the Schedule of Procedures/Assessments (Table 5).

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, withdrawal of consent, 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.

A subject removed from the study for any reason may be replaced.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

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 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.

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. Statistical analyses will be performed using SAS software or other validated statistical software as required.

Descriptive statistics will be presented including mean and standard deviation of photosensitivity range for each subject at Screening and at each time point, for each Treatment visit day by treatment group. Graphical displays of the data for each subject will allow exploration of intersubject and intrasubject variability. Details of statistical methods and analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of 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

The reduction in PPR response will be evaluated for 8 hours postdose for the entire time period. A diminution in response is anticipated with the dose range. A statistical difference of treatment doses versus placebo will be evaluated.

The primary endpoint, the change in the PPR range, is evaluated using mixed effects model for comparing low and high treatment doses versus placebo. Another endpoint will include proportions of subjects responding to treatment versus placebo. Most patients have strong responses to effective treatments compared to placebo, which can be evaluated by graphs of partial response (ie, 3 steps narrowing) and abolition of PPR.

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of this study is the mean change from baseline in the PPR range in each subject's most sensitive eye condition at each dose level of E2730 as compared to placebo.

9.7.1.1.2 SECONDARY ENDPOINTS

- Mean changes from baseline in PPR ranges in each subject's eye closure, eyes closed, and eyes open condition at each dose level of E2730 as compared to placebo
- Onset, maximum change, and duration of photosensitivity response at each dose level in all 3 eye conditions at the time course of E2730 as compared to placebo
- Frequency and percentage of subjects with Complete Suppression, Partial Response, and no Response of PPR at each dose level of E2730 as compared to placebo
- Occurrence of AEs or changes in the neurological examination after single doses of E2730 compared to placebo
- Changes in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2730 compared to placebo
- PK of E2730 and its N-acetyl metabolite, M1
- Relationship between PK parameters of E2730 onset, maximum change, and duration of impact on photosensitivity

9.7.1.2 Definitions of Analysis Sets

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

The Pharmacokinetic Analysis Set is the group of randomized subjects who receive at least 1 dose of study drug and have sufficient PK data to derive at least 1 PK parameter.

The Pharmacodynamic Analysis Set is the group of randomized subjects who receive at least 1 dose of study drug and have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened and the number failing screening (overall and by reason for failure) will be summarized. Screen failure data will be listed. The number of subjects randomized along with the number of subjects administered each dose of E2730 will also be presented.

Subjects who prematurely terminate their participation in the study will be summarized by their primary reason for study termination.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized by dose group for each part of the study using descriptive statistics. Continuous demographic and baseline variables include age, height, and weight; categorical variables include sex, age group, 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 by treatment group, Anatomical Therapeutic Chemical (ATC) class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the dose of study drug. Concomitant medications will be defined as medications that started after the date of the dose of study drug up to 28 days after the subject's dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

Not applicable.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, CCI Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK Analysis Set will be used for listings of individual E2730 and M1 plasma concentrations, summaries and listings of PK parameters. Plasma concentrations will be tabulated by nominal sampling time and summarized by treatment dose using summary statistics.

The following PK parameters will be derived by noncompartmental analysis using plasma concentrations of E2730 and M1. These parameters will include, but are not limited to:

- C_{max} maximum observed concentration
- $AUC_{(0-8h)}$ area under concentration x time curve from time 0 to 8 hours postdose
- t_{max} time to reach C_{max} following drug administration

The PK of E2730 will be analyzed based on available data from this study. The PK and PD Analysis datasets will be used to evaluate the relationship of PK of E2730 and change in PPR response. The PK-PD analyses may include the examination of the relationship of PK of E2730 and PPR response (eg, time of onset, maximum change, and duration of PPR; Bond and Lader data) using model-based approaches.

Analysis variables: Plasma concentrations of E2730 and *N*-acetyl metabolite (M1)

Analysis set: The Pharmacokinetic Analysis Set will be used for individual plasma concentration listings and summaries of plasma concentrations.

Analysis methods: The PK of E2730 will be analyzed based on available data from this study. Plasma concentrations will be tabulated by nominal sampling time and summarized by treatment dose using summary statistics.

9.7.1.7.2 PHARMACODYNAMIC, CCI [redacted] ANALYSES

The PD analysis will be performed on the PD Analysis Set.

No multiplicity adjustments will be made. The 5 PPR measured postdose on a study day will be averaged and used for the primary endpoint. The predose PPR data from the respective treatment period will be used as the baseline data.

The primary and secondary endpoints of mean change from baseline of the average PPR for each E2730 dose compared with placebo in the most sensitive and different eye conditions will be performed using a mixed effects model for crossover study. The model will include treatment, period, and sequence as fixed effects, baseline (predose) measurement as a covariate, and subject nested within sequence as a random effect. Where data are normally distributed, least squares (LS) means, difference in LS means of each E2730 dose compared to placebo, and 90% CIs will be presented with no adjustments for multiplicity.

Additional analysis by graphical exploration on onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions at the time course of E2730 as compared to placebo. This analysis will provide further information on the frequency and percentage of subjects with Complete Suppression, Partial Response, and No Response of PPR at each dose level of E2730 as compared to placebo.

Sensitivity analyses for PPR may be conducted, for example, of PPR for subjects who completed Treatment Periods 1-3 versus those who are included in the PD Analysis Set. CCI [redacted] All PD data (Bond and Lader) will be listed and summarized by treatment, as appropriate, using standard summary statistics. Descriptive summary statistics (eg, mean, SD, median, minimum, and maximum

for continuous variables, and the number and percent for categorical variables) of each endpoint and the changes from baseline will be tabulated.

CCI [redacted]

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and neurological/physical examinations. Treatment-emergent adverse events (TEAEs) will be summarized by presenting for each treatment group, the incidence of AEs.

An assessment of suicidal ideation and behavior using the C-SSRS will be performed throughout the study.

Descriptive summary statistics (eg, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent for categorical variables) of the laboratory, vital signs, and ECG parameters, and changes from baseline will be evaluated by treatment group. The proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors will be summarized.

9.7.1.8.1 Extent of Exposure

Extent of exposure will be presented by dose level.

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 20.0 or higher) lower level term (LLT) 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, using the Safety Analysis Set. 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]). A subject data listing of all SAEs, including deaths, will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, 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 Section 9.5.1.5.3 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 also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) 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 was 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 may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

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

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia during the treatment period will be summarized. Clinically abnormal ECG results in QTc Fridericia will be categorized as follows:

- For the QT interval assessment, clinically abnormal ECG results for QT interval corrected for heart rate using Fridericia's formula (QTcF) will be categorized as follows: QTcF values >450 msec, >480 msec, and >500 msec, and time-matched change from baseline in QTcF >30 msec and >60 msec.

9.7.1.8.6 OTHER SAFETY ANALYSES

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

9.7.2 Determination of Sample Size

Approximately 9 subjects with photosensitive epilepsy and a stable PPR will be needed to be randomized in the study in order to obtain 6 evaluable subjects. Based on a similar study in subjects with photosensitive epilepsy (NCT02564029), an estimated standard deviation of the treatment group difference of the SPR in the subject's most sensitive eye condition is 3.62. The width of a 90% CI of the mean group difference based on this standard deviation assumption and 6 subjects is 2.431. Therefore, a sample size of 6 would be sufficient to detect a mean group difference of 3 or larger with 90% confidence.

9.7.3 Interim Analysis

No formal 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.

10 REFERENCE LIST

CCI [redacted]

Bond A, Lader M. The use of analogue scales in rating subjective feelings. Br. J. med. Psychol. 1974; 47: 211-8.

CCI [redacted]

Kasteleijn-Nolst Trenité DG, Marescaux C, Stodieck S, Edelbroek PM, Oosting J. Photosensitive epilepsy: a model to study the effects of antiepileptic drugs. Evaluation of the piracetam analogue, levetiracetam. Epilepsy Res. 1996;25:225-30.

Löscher W, Luna-Tortós C, Römermann K, Fedrowitz M. Do ATP-binding cassette transporters cause pharmacoresistance in epilepsy? Problems and approaches in determining which antiepileptic drugs are affected. Curr Pharm Des. 2011;17(26):2808-28.

CCI [redacted]

Columbia-Suicide Severity Rating Scale (C-SSRS). Columbia University. Available from: http://www.cssrs.columbia.edu/scales_cssrs.html

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 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 and the Competent Authorities 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 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 interactive response system, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, 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 correction 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.

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 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an

ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

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 drugs 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, or upon notification of the sponsor, 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 – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
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×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L 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	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<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 – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Prohibited Concomitant Medications

Prohibited Concomitant Medication
CCI
The above list of prohibited concomitant medications is not exhaustive. The investigator should provide further guidance before switching any of the concomitant medications mentioned in the above list.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2730-A001-201

Study Protocol Title: A Multicenter, Double-Blind, Randomized, Cross-Over Study Evaluating Pharmacodynamic Activity of E2730 in Adult Subjects with Photosensitive Epilepsy

Investigational Product Name: E2730

IND Number: 124728

SIGNATURES

Authors:

PPD

Eisai, Inc. Date

PPD

Eisai, Inc. Date

PPD

Eisai, Inc. Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2730-A001-201
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Cross-Over Study Evaluating Pharmacodynamic Activity of E2730 in Adult Subjects with Photosensitive Epilepsy
Investigational Product Name:	E2730
IND Number:	124728

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.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2730-A001-201
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Cross-Over Study Evaluating Pharmacodynamic Activity of E2730 in Adult Subjects with Photosensitive Epilepsy
Sponsor:	Eisai Inc. 100 Tice Boulevard, Woodcliff Lake, New Jersey 07677, US
Investigational Product Name:	E2730
Indication:	Not applicable
Phase:	2
Approval Date:	V1.0 30 May 2018 (original protocol)
IND Number:	124728
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.: E2730

Name of Active Ingredient: CCI [redacted]

Study Protocol Title

A Multicenter, Double-Blind, Randomized, Cross-Over Study Evaluating Pharmacodynamic Activity of E2730 in Adult Subjects with Photosensitive Epilepsy

Principal Investigator

PPD

Sites

Approximately 6 sites in the US

Study Period and Phase of Development

The total study duration from first subject enrolled to last subject's last visit/last assessment will be approximately 4 to 5 months.

Phase 2

Objectives

Primary Objective

- To assess the pharmacodynamic (PD) activity of E2730 as measured by suppression of epileptic photoparoxysmal response (PPR) in the subject's most sensitive eye condition as a proof of principle of efficacy in subjects with photosensitive epilepsy

Secondary Objectives

- To assess the PD activity of E2730 as measured by suppression of epileptic PPR, onset, maximum change, and duration of response in 3 eye-conditions (eye closure, eyes closed, and eyes open) in subjects with photosensitive epilepsy.
- To assess the safety and tolerability of E2730 following a single oral dose in subjects with photosensitive epilepsy
- To assess the pharmacokinetics (PK) of E2730 following a single oral dose in subjects with photosensitive epilepsy
- To evaluate potential exposure-PD response relationships

CCI [redacted]

- CCI [redacted]

Study Design

This is a multicenter, double-blind, randomized, 6-sequence, 3-treatment, 3-period cross-over study in adult subjects with epilepsy. This study will use the photosensitivity proof of principle model to determine the potential of E2730 to reduce the photosensitive range in adult subjects. This study will have 2 phases: Prerandomization and Randomization. The Prerandomization Phase will consist of a Screening Period (up to 3 weeks), during which each subject's study eligibility will be determined

and baseline assessments will be conducted. The Randomization Phase will consist of 3 Treatment Periods with a single dose in each period (placebo, E2730 40 mg, or E2730 120 mg, each separated by a 3-week (±3 days) washout interval for a total of approximately 6 weeks), and a Follow-up Period (a single visit, 3 weeks ±3 days after the last day of study product administration). All visits will be conducted on an outpatient basis.

At the Screening Visit (Visit 1), subjects will undergo an electroencephalogram intermittent photic stimulation (EEG-IPS) assessment in 3 eye-conditions (eye closure, eyes closed, and eyes open) at ascending and then descending photo-stimulation frequencies. The Screening Visit EEG-IPS assessment will be performed at 5 time points, over an approximately 4-hour time period (0, 1, 2, 3, and 4 hours; within ±15 minutes of the scheduled time point). Subjects with a reproducible PPR on EEG of at least 3 points on the standardized photosensitivity response (SPR) scale in at least 1 eye condition on at least 3 of the EEGs performed at Screening will be eligible for the study. The baseline assessments will be conducted, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency for each eye condition. Qualified medical personnel for the management of acute seizures will be present during the day of EEG-IPS procedure throughout the duration of the study.

Within 21 days of the Screening Visit (Visit 1), subjects will be asked to return to the study site for Visit 2 (Day 1), when the final determination of eligibility will be made. Subjects will be randomized, enter the Randomization Phase, and will begin Treatment Period 1.

Subjects meeting eligibility criteria will be randomized into 1 of 6 treatment sequences to receive, in a blinded fashion, a single oral dose of placebo control, E2730 40 mg, or E2730 120 mg and begin the Randomization Phase. On the day of each Treatment Visit (ie, Day 1, Day 22, Day 43), subjects will arrive at the clinic in the morning following an overnight fast of at least 8 hours, and the baseline assessments will be conducted again at predose, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency for each eye condition. Study drug product will be administered with approximately 240 mL (8 fluid ounces) of water. Additional water may be provided in increments of 50 mL (up to a maximum of 100 mL), if required. A light snack can be provided at 2 hours postdose. Water will be permitted ad libitum except from the time of dosing until 1 hour postdose. Each treatment period will be separated by a 3-week (±3 days) washout interval.

The safety, tolerability, and PK of E2730 will be assessed. A full neurological examination and vital signs evaluation will be performed at screening and a brief neurological examination will be performed at predose and at scheduled time points after dosing. E2730 activity will be characterized by EEG-IPS, for a minimum of 2.5 minutes under all eye conditions (eye closure, eyes open, and eyes closed) on each treatment day. EEG-IPS sessions will be assessed on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4) at 30 minutes to 2 hours predose and 1, 2, 4, 6, and 8 hours postdose time points. The Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered at screening, postdose at the end of every treatment visit, and at the Follow-up/Early discontinuation visit. Bond and Lader scale for central nervous system (CNS)–related sedative adverse effects will be measured for each subject at predose, 1, 2, 4, 6, and 8 hours postdose at every visit. There will be an interval of 21±3 days between scheduled subsequent visits between dosing days.

After completing Treatment Period 3, all subjects will enter the Follow-up period during which they will be required to complete a Follow-up visit at 3 weeks ±3 days following the last day of study product administration. The end of study is defined as the last subject completing the Follow-up Visit. The anticipated study participation duration for each subject is approximately 12 weeks.

Early Discontinuation

Subjects who discontinue study drug before completing all treatments in the study, for any reason, will undergo an Early Discontinuation (ED) Visit within 3 weeks ±3 days of their last dose of study drug.

Number of Subjects

Approximately 9 subjects will be randomized to achieve 6 evaluable subjects. Subjects who discontinue from the study early may be replaced, after consultation with the sponsor.

Inclusion Criteria

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

1. Male or female 18 to 60 years of age at the time of informed consent.
2. A diagnosis and history of a PPR on EEG with or without a diagnosis of epilepsy.
3. Currently taking up to a maximum of 3 concomitant antiepileptic drugs (AEDs). If taking concomitant AED(s), the dose must have remained stable for at least 4 weeks prior to screening.
4. A reproducible IPS-induced PPR on EEG of at least 3 points on a frequency assessment scale (SPR) in at least 1 eye condition on at least 3 of the EEGs performed at Screening.
5. A body mass index (BMI) between 18 to 35 kg/m^2 and a total body weight greater than or equal to 45 kg at the time of Screening.
6. Agrees to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period prior to each treatment day.
7. Willing and able to comply with all aspects of the protocol.

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 [ß-hCG] *(*or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). 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:
   a. Within 30 days before study entry, have had unprotected sexual intercourse and did not use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia)
   b. 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. If currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 28 days after study drug discontinuation. Females who are using hormonal contraceptives must be on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 28 days after study drug discontinuation.

   NOTE: All 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. Male subjects who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.
4. History of nonepileptic seizures (eg, metabolic, structural, or pseudoseizures) while on any antiepileptic medication(s).
5. History of status epilepticus while on any antiepileptic medication(s) within 2 years prior to Screening.
6. Ongoing or history of generalized tonic-clonic seizures within 6 months prior to Screening.
7. Previously developed or who experienced a clinical seizure during prior PPR assessment or screening IPS procedure, respectively.
8. CCI [redacted]
9. Multiple drug allergies or a severe drug reaction to AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
10. Current evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) with the exception of epilepsy, which in the opinion of the investigator could affect the subject's safety or interfere with the study assessments.
11. An active CNS infection, demyelinating disease, degenerative neurological disease or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results.
12. Current evidence of clinically significant active liver disease, porphyria, or with a family history of severe hepatic dysfunction indicated by abnormal liver function tests greater than 3 times the upper limit of normal (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).
13. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening.
14. Known to be human immunodeficiency virus (HIV) positive.
15. History of drug or alcohol dependency or abuse within the 12 months before Screening, or those who have a positive drug test or alcohol test at Screening.
16. Concomitant use of cannabinoids.
17. Inability to follow restriction on watching television, or use of any device with an animated screen (ie, computer, video games, tablets) 24 hours before dosing.
18. A history of prolonged QT syndrome or risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome), or the use of concomitant medications that prolonged the QT/corrected QT (QTc) interval; or prolonged QT/QTc interval (QTc >450 msec) demonstrated on ECG at Screening or Baseline (based on average of triplicate ECGs).
19. Any suicidal ideation with intent with or without a plan within 6 months before Screening or during Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS).
20. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS).

21. Any psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years.
22. Currently enrolled in another clinical study or used any investigational drug or device within 30 days or 5 half-lives, whichever is longer, preceding informed consent, except the investigational study for the evaluation of commercial IPS machine.
23. Frequent spontaneous background burst or current evidence of proconvulsive activity on EEG (eg, increase in spike-wave activity) at Screening.

Study Treatments

Test Drug: E2730

E2730 will be supplied as active pharmaceutical ingredient in capsule at dose strengths of 40 mg and 80 mg.

Comparator Drug: E2730-matched placebo

Each subject will receive a single oral dose of E2730 40 mg, E2730 120 mg, and matched-placebo in a cross-over sequence according to his/her randomization code.

E2730 40 mg: 1 E2730 40 mg capsule and 1 E2730-matched placebo capsule

E2730 120 mg: 1 E2730 80 mg capsule and 1 E2730 40 mg capsule

Placebo: 2 E2730-matched placebo capsules

Duration of Treatment

Single dose (ie, the Randomization Phase will consist of 3 Treatment Periods with a single dose in each period)

Concomitant Drug/Therapy

Up to 3 concomitant AEDs are allowed during the course of the study, provided that the dosage of concomitant AED(s) has remained stable for at least 4 weeks prior to Screening. During the study, changes to concomitant AEDs (including dosage) are not permitted.

Assessments

Efficacy Assessments

Not applicable

Pharmacokinetic Assessments

Blood samples for the determination of E2730 plasma concentrations and its *N*-acetyl metabolite (M1) will be collected at predose and postdose at 1, 2, 4, 6, and 8 hours on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4). In case of early discontinuation, a PK sample will be taken.

Pharmacodynamic Assessments

PD activity of E2730 will be assessed by suppression of PPR following IPS under 3 conditions (eye closure, eyes closed, and eyes open) using the Grass PS 33 photic stimulator with an unpatterned glass lamp and an intensity of 100cd/m^2/flash at 30 minutes to 2 hours predose, and at 1, 2, 4, 6, and 8 hours postdose. The time course (30 minutes to 2 hours predose to 8 hours postdose) will help assess the onset, maximum change, and duration of the reduction in PPR response. PPR is expected to be within the range from 2 Hz to 60 Hz, depending on subject sensitivity to IPS.

The Bond and Lader Visual Analogue Scale (VAS) for CNS–related sedation effects will be measured for each subject at predose, 1, 2, 4, 6, and 8 hours postdose on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4).

All PD assessments will be performed within ±15 minutes of the scheduled time point.

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Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs); laboratory evaluation for hematology, blood chemistry, and urine values; measurement of vital signs and ECGs; and the performance of neurological and physical examinations.

An assessment of suicidality using the C-SSRS will be performed at Screening, during each Treatment visit (postdose), and at the Follow-up/ED Visit.

Other Assessments

Not applicable

Bioanalytical Methods

Plasma concentrations of E2730 and the *N*-acetyl metabolite (M1) will be measured using validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods.

Statistical Methods

Descriptive statistics will be presented including mean and standard deviation of photosensitivity range for each subject at Screening and at each time point, for each Treatment visit day by treatment group. Graphical displays of the data for each subject will allow exploration of intersubject and intrasubject variability.

Details of statistical methods and analyses will be specified in the statistical analysis plan (SAP).

Study Endpoints

Primary Endpoint

Mean change from baseline in the PPR range in each subject's most sensitive eye condition at each dose level of E2730 as compared to placebo

Secondary Endpoints

- Mean changes from baseline in PPR ranges in each subject's eye closure, eyes closed, and eyes open condition at each dose level of E2730 as compared to placebo
- Onset, maximum change, and duration of photosensitivity response at each dose level in all 3 eye conditions at the time course of E2730 as compared to placebo
- Frequency and percentage of subjects with Complete Suppression, Partial Response, and no Response of PPR at each dose level of E2730 as compared to placebo
- Occurrence of AEs or changes in the neurological examination after single doses of E2730 compared to placebo
- Changes in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2730 compared to placebo
- PK of E2730 and its *N*-acetyl metabolite, M1
- Relationship between PK parameters of E2730 onset, maximum change, and duration of impact on photosensitivity

Analysis Sets

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

The Pharmacokinetic Analysis Set is the group of randomized subjects who receive at least 1 dose of study drug and have sufficient PK data to derive at least 1 PK parameter.

The Pharmacodynamic Analysis Set is the group of randomized subjects who receive at least 1 dose of study drug and have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

Not Applicable

Pharmacokinetic, Pharmacodynamic, CCI Analyses

Pharmacokinetic Analyses

The PK Analysis Set will be used for listings of individual E2730 and *N*-acetyl metabolite (M1) plasma concentrations, summaries and listings of PK parameters. Plasma concentrations will be tabulated by nominal sampling time and summarized by treatment dose using summary statistics.

The following PK parameters will be derived by noncompartmental analysis using plasma concentrations of E2730 and M1. These parameters will include, but are not limited to:

C_{max} maximum observed concentration

$AUC_{(0\text{-}8h)}$ area under concentration x time curve from time 0 to 8 hours postdose

t_{max} time to reach C_{max} following drug administration

The PK of E2730 will be analyzed based on available data from this study. The PK and PD Analysis datasets will be used to evaluate the relationship of PK of E2730 and change in PPR response. The PK-PD analyses may include the examination of the relationship of PK of E2730 and PPR response (eg, time of onset, maximum change, and duration of PPR; Bond and Lader data) using model-based approaches.

Pharmacodynamic Analyses

The PD analysis will be performed on the PD Analysis Set.

No multiplicity adjustments will be made. The 5 PPR measured postdose on a study day will be averaged and used for the primary endpoint. The predose PPR data from the respective treatment period will be used as the baseline data.

The primary and secondary endpoints of mean change from baseline of the average PPR for each E2730 dose compared with placebo in the most sensitive and different eye conditions will be performed using a mixed effects model for crossover study. The model will include treatment, period, and sequence as fixed effects, baseline (predose) measurement as a covariate, and subject nested within sequence as a random effect. Where data are normally distributed, least squares (LS) means, difference in LS means of each E2730 dose compared to placebo, and 90% CIs will be presented with no adjustments for multiplicity.

Additional analysis by graphical exploration on onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions at the time course of E2730 as compared to placebo. This analysis will provide further information on the frequency and percentage of subjects with Complete Suppression, Partial Response, and No Response of PPR at each dose level of E2730 as compared to placebo.

Sensitivity analyses for PPR may be conducted, for example, of PPR for subjects who completed Treatment Periods 1-3 versus those who are included in the PD Analysis Set. CCI

All PD data (Bond and Lader) will be listed and summarized by treatment, as appropriate, using standard summary statistics. Descriptive summary statistics (eg, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent for categorical variables) of each endpoint and the changes from baseline will be tabulated.

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Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and neurological/physical examinations. Treatment-emergent adverse events (TEAEs) will be summarized by presenting for each treatment group, the incidence of AEs. An assessment of suicidal ideation and behavior using the C-SSRS will be performed throughout the study.

Descriptive summary statistics (eg, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent for categorical variables) of the laboratory, vital signs, ECG parameters, and changes from baseline will be evaluated by treatment group. The proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors will be summarized.

Interim Analyses

No formal interim analysis is planned.

Sample Size Rationale

Approximately 9 subjects with photosensitive epilepsy and a stable PPR will be needed to be randomized in the study in order to obtain 6 evaluable subjects. Based on a similar study in subjects with photosensitive epilepsy (NCT02564029), an estimated standard deviation of the treatment group difference of the SPR in the subject's most sensitive eye condition is 3.62. The width of a 90% CI of the mean group difference based on this standard deviation assumption and 6 subjects is 2.431. Therefore, a sample size of 6 would be sufficient to detect a mean group difference of 3 or larger with 90% confidence.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{(0-24)}$	area under the concentration-time curve from 0 time to fixed time 24 hours
$AUC_{(0-inf)}$	area under the concentration-time curve from 0 time extrapolated to infinity time
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variance
ED	Early Discontinuation (Visit)
EEG-IPS	electroencephalogram intermittent photic stimulation
CCI	[redacted]
GM	geometric mean
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPS	intermittent photic stimulation
IRB	Institutional Review Board
LNH	low/normal/high
LS	least squares
M1	E2730 N-acetyl metabolite
MedDRA	Medical Dictionary for Regulatory Activities
Max	maximum
Min	minimum
n/a	not applicable

Abbreviation	Term
PD	pharmacodynamic
CCI	[redacted]
PI	principal investigator
PK	pharmacokinetics
POC	proof-of-concept
PPR	photoparoxysmal response
PT	preferred term
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAD	single ascending dose
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
SPR	standardized photosensitivity response
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
$t_{1/2}$	terminal elimination phase half-life
t_{max}	time at which the highest drug concentration occurs
VAS	Visual Analogue Scale

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), 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 (Code of Federal Regulations [CFR], Title 21 CFR Parts 50 and 56). Any protocol amendment or revision to the ICF 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.

A signed letter of study approval from the IRB chairman must be sent to the principal investigator (PI) 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 the 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 will forward a copy to the sponsor at the time of each periodic report. The investigator 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.

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 and Competent Authority within 15 calendar days, 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 (SOP) 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
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use

- Title 21 of the United States Code of Federal Regulations (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 document, the investigator must explain to each subject 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, and the extent of maintaining confidentiality of the subject's records. Each subject 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 treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject 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, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject 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 will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained. CCI [redacted]

An unsigned copy of an IRB-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject 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 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 6 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 organizations (CROs) will be provided to each site.

7 INTRODUCTION

7.1 Indication

The initial goal is to develop E2730 as an antiepileptic drug (AED) in patients with a rare form of epilepsy, in parallel with partial-onset seizure studies in adolescents and adults. The selection of the disease candidate for orphan drug treatment will be based on ongoing and planned preclinical studies in house and at external institutions.

7.1.1 Mechanism of Action – E2730

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7.1.2 Clinical Experience With E2730

The E2730 clinical program to date comprises 1 completed Phase 1 study in which 6 healthy subjects received single doses of E2730 (20 mg) and 2 healthy subjects received placebo. The first-in-human single ascending dose (SAD) study of E2730 (E2730-A001-001; Study 001), was initially planned to administer E2730 with dose escalation conducted in sequential dose groups consisting of 8 subjects per group randomized (3:1) to receive single ascending E2730 doses of 20, 40, or 80 mg or E2730-matched placebo. Dose escalation could only occur if the available data supported an increase in dose that did not exceed plasma E2730 exposures predefined for Cmax=1.5 µg/mL or area under the concentration-time curve from zero time extrapolated to infinite time (AUC(0-inf))=20µg•h/mL. This threshold was originally required by the Food and Drug Administration (FDA) and was reached with the first E2730 dose (20 mg). Thus, no higher E2730 doses were administered.

The SAD study (E2730-A001-002; Study 002) is currently ongoing, where doses of 40, 80, 120, and 160 mg are planned in healthy subjects. The proposed doses are anticipated not to exceed 3 μg/mL, per the FDA's revised limit on the Cmax, and the data will be evaluated on an ongoing basis during each dose escalation. The anticipated Cmax of the highest dose cohort (120 mg cohort) in the current study is likely not to exceed the prespecified threshold.

7.1.2.1 Pharmacokinetics

In Study 001 and Study 002, which enrolled healthy subjects (18-50 years); E2730 was rapidly absorbed after a single oral administration of 20, 40, 80, and 120 mg. Plasma E2730 concentrations peaked at 1.25 to 5.5 hours. The *N*-acetyl metabolite (M1) was sparsely detected just above or at the lower limit of quantification, thus a complete plasma M1 pharmacokinetic (PK) profile could not be derived. Pharmacokinetic parameters in Study 001 and Study 002 are shown in Table 1. Although C_{max} and $AUC_{(0-24)}$ were less than dose proportional between 20 mg and 40 mg, there was almost dose proportional from 40 mg through 120 mg. The highest individual C_{max} value (2.930 μg/mL) of 120 mg was not to exceed the prespecified threshold of 3 μg/mL. There was 1 subject who had low plasma E2730 concentration (C_{max}: 0.222 μg/mL) in the 120 mg cohort. The plasma E2730 concentration declined with a mean terminal elimination phase half-life ($t_{1/2}$) of 59.0 to 69.8 hours.

Table 1 PK Parameters In Study 001 (20 mg) and Study 002 (40 mg, 80 mg, and 120 mg)

Dose	t_{max} (h)	C_{max} (ng/mL)	$AUC_{(0-24)}$ (ng•h/mL)	$AUC_{(0-inf)}$ (ng•h/mL)	$t_{½}$ (h)
20 mg	1.25 (0.50, 1.50)	351 (22.7)	6330 (23.9)	28600 (11.5)	69.8 (21.9)
40 mg	3.00 (1.50, 6.00)	496 (20.3)	9210 (19.6)	41300 (15.9)	69.7 (15.2)
80 mg	5.50 (1.00, 8.00)	899 (14)	16900 (12.7)	61100 (6.44)	59.0 (15.8)
120 mg	4.50 (0.50, 8.00)	1270 (116)	23300 (110)	n/a[a]	n/a[a]

$AUC_{(0-24)}$ = area under the concentration-time curve from 0 time to fixed time 24 hours; $AUC_{(0-inf)}$ = area under the concentration-time curve from 0 time extrapolated to infinity time; PK = pharmacokinetics, max = maximum; min = minimum; $t_{1/2}$ = terminal elimination phase half-life; t_{max} = time at which the highest drug concentration occurs, n/a = not applicable; CV = coefficient of variance.

Note: All PK parameters, except t_{max}, are presented as geometric mean (%CV). t_{max} is presented as median (min, max).

a. As of the data cut-off date of 22 May 2018, plasma concentrations of E2730 at 120 mg are available until 24 hours post dose.

After administration of E2730 20 mg, the GM percent of recovered parent drug in urine collected up to 96 hours postdose was 21.8% and a smaller fraction (GM=0.728%) was excreted as M1.

7.1.2.2 Safety and Tolerability

E2730 was well tolerated in healthy adult subjects when administered as single oral doses across the dose range of 20 to 120 mg (Study 001 and Study 002). The maximum tolerated dose (MTD) has not yet been reached (Study 002).

Among 6 subjects who received 20 mg E2730 (Study 001), 1 subject experienced a TEAE (postural orthostatic tachycardia syndrome) on the day of administration. The event was mild in severity and resolved on the same day without treatment. The investigator judged the event to be related to the study drug. Another subject experienced a TEAE (dizziness) on the day of placebo administration. The event was mild in severity and resolved on the same day without treatment. The investigator judged the event to be related to the study drug.

From the blinded preliminary safety results in 40 mg and 80 mg, 4 subjects experienced 6 TEAEs (sleepiness, insomnia, nausea, drowsiness [2 subjects], and decrease appetite) and 4 subjects experienced 8 TEAEs (orthostatic tachycardia [2 subjects], dermatitis contact, atrioventricular block, dizziness, headache, insomnia, and diarrhea), respectively. There were no medically significant findings from vital signs in 40 mg and 80 mg cohorts.

In the 120 mg cohort, the safety data have been reviewed through Day 13. Clinically significant findings in vital signs were reported for 2 subjects, which were characterized as AEs of orthostatic tachycardia and hypotension. Both AEs were mild and in both cases, subjects were asymptomatic. There were no deaths or SAEs, and no medically significant findings have been reported from EEG or ECG (no significant QT or QTc prolongations). There have been no clinically significant laboratory abnormalities. There were no epileptiform discharges or clinically significant abnormalities of EEG observed in the 40 mg, 80 mg, or 120 mg dose cohorts.

7.2 Study Rationale

7.2.1 Photosensitivity Proof of Concept Model

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8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to assess the PD activity of E2730 as measured by suppression of epileptic PPR in the subject's most sensitive eye condition as a proof of principle of efficacy in subjects with photosensitive epilepsy.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the PD activity of E2730 as measured by suppression of epileptic PPR, onset, maximum change, and duration of response in 3 eye-conditions (eye closure, eyes closed, and eyes open) in subjects with photosensitive epilepsy.

- To assess the safety and tolerability of E2730 following a single oral dose in subjects with photosensitive epilepsy.
- To assess the PK of E2730 following a single oral dose in subjects with photosensitive epilepsy.
- To evaluate potential exposure-PD response relationships.

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9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, double-blind, randomized, 6-sequence, 3-treatment, 3-period cross-over study in adult subjects with epilepsy. This study will use the photosensitivity proof of principle model to determine the potential of E2730 to reduce the photosensitive range in adult subjects. This study will have 2 phases: Prerandomization and Randomization. The Prerandomization Phase will consist of a Screening Period (up to 3 weeks), during which each subject's study eligibility will be determined and baseline assessments will be conducted. The Randomization Phase will consist of 3 Treatment Periods with a single dose in each period (placebo, E2730 40 mg, or E2730 120 mg, each separated by a 3-week (±3 days) washout interval for a total of approximately 6 weeks), and a Follow-up Period (a single visit, 3 weeks ±3 days after the last day of study product administration). All visits will be conducted on an outpatient basis.

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

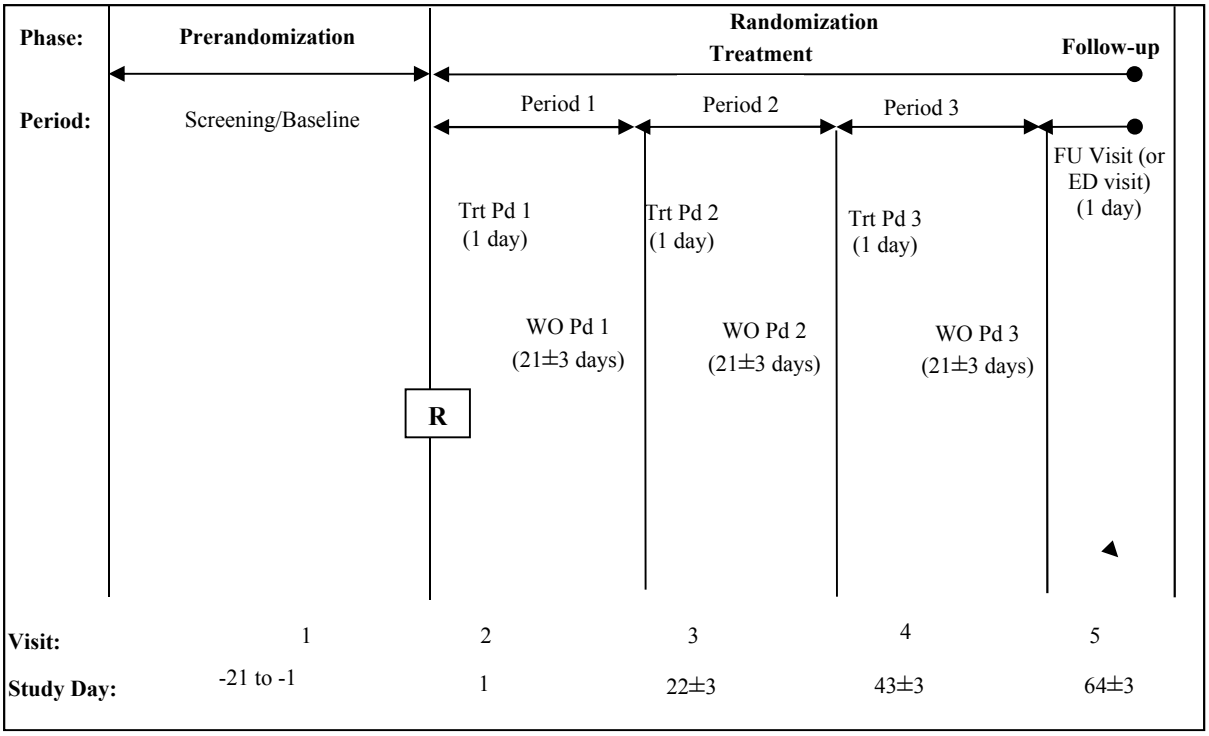

Figure 1 Study Design for a Crossover Study

ED = Early discontinuation, FU = Follow Up, Pd = period, R = randomization, Trt = treatment, WO = washout

9.1.1 Prerandomization Phase

The Prerandomization Phase will consist of a Screening Period (up to 3 weeks), during which each subject's study eligibility will be determined and baseline assessments will be conducted.

9.1.1.1 Screening Period

Screening will occur between Day –21 and Day –1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis and history of a PPR on EEG with or without a diagnosis of epilepsy for which they are receiving up to 3 concomitant AEDs.

The Screening Disposition case report form (CRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

At the Screening Visit (Visit 1), subjects will undergo an EEG-IPS assessment in 3 eye-conditions (eye closure, eyes closed, and eyes open) at ascending and then descending photo-stimulation frequencies. The Screening Visit EEG-IPS assessment will be performed at 5 time points, over an approximately 4-hour time period (0, 1, 2, 3, and 4 hours; within ±15 minutes of the scheduled time point). Subjects with a reproducible PPR on EEG of at least 3 points on the SPR scale in at least 1 eye condition on at least 3 of the EEGs performed at Screening will be eligible for the study. The baseline assessments will be conducted, including determination of the lower and upper limit of photosensitivity to intermittent photic stimulation (EEG-IPS) threshold frequency for each eye condition. Qualified medical personnel for the management of acute seizures will be present during the day of EEG-IPS procedure throughout the duration of the study.

9.1.2 Randomization Phase

The duration of the Randomization Phase will be 9 weeks and will include 3 Treatment Periods (placebo, E2730 40 mg or E2730 120 mg, each separated by a 3-week (±3 days) washout interval, for a total of approximately 6 weeks), and a Follow-up Period (a single visit, 3 weeks ±3 days after the last day of study product administration). Subjects whose screening assessments and evaluations (including Day 1 [Visit 2] procedures) are completed and reviewed by the investigator and who continue to meet all of the inclusion/exclusion criteria will enter the Randomization Phase. The baseline assessments will be conducted again at predose of each Treatment Period, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency for each eye condition.

9.1.2.1 Treatment Periods

Subjects will be randomized into 1 of 6 treatment sequences to receive placebo, E2730 40 mg, or E2730 120 mg. Each of the 3 treatment periods will be separated by a 3-week (±3 days) washout interval.

9.1.2.2 Follow-up Period

After completing Treatment Period 3, all subjects will enter the Follow-up period during which they will be required to complete a Follow-up visit. The Follow-up Period is a single visit, 3 weeks ±3 days after the last day of study product administration.

9.2 Discussion of Study Design, Including Choice of Control Groups

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 9 subjects will be randomized to achieve 6 evaluable subjects at approximately 6 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 18 to 60 years old at the time of informed consent.
2. A diagnosis and history of a PPR on EEG with or without a diagnosis of epilepsy.
3. Currently taking up to a maximum of 3 concomitant antiepileptic drugs (AEDs). If taking concomitant AED(s), the dose must have remained stable for at least 4 weeks prior to screening.
4. A reproducible IPS-induced PPR on EEG of at least 3 points on a frequency assessment scale (SPR) in at least 1 eye condition on at least 3 of the EEGs performed at Screening.
5. A body mass index (BMI) between 18 to 35 kg/m^2 and a total body weight greater than or equal to 45 kg at the time of Screening.
6. Agrees to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period prior to each treatment day.
7. Willing and able to comply with all aspects of the protocol.

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 [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). 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:
   a) Within 30 days before study entry, have had unprotected sexual intercourse and did not use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia)
   b) 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. If

currently abstinent, the subject must agree to use a double barrier method as described above if she becomes sexually active during the study period or for 28 days after study drug discontinuation. Females who are using hormonal contraceptives must be on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 28 days after study drug discontinuation.

NOTE: All 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. Male subjects who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period and for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.
4. History of nonepileptic seizures (eg, metabolic, structural, or pseudoseizures) while on any antiepileptic medication(s).
5. History of status epilepticus while on any antiepileptic medication(s) within 2 years prior to Screening.
6. Ongoing or history of generalized tonic-clonic seizures within 6 months prior to Screening.
7. Previously developed or who experienced a clinical seizure during prior PPR assessment or screening IPS procedure, respectively.
8. CCI [redacted]
9. Multiple drug allergies or a severe drug reaction to AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
10. Current evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) with the exception of epilepsy, which in the opinion of the investigator could affect the subject's safety or interfere with the study assessments.
11. An active central nervous system (CNS) infection, demyelinating disease, degenerative neurological disease or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results.
12. Current evidence of clinically significant active liver disease, porphyria, or with a family history of severe hepatic dysfunction indicated by abnormal liver function tests greater than 3 times the upper limit of normal (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).
13. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening.
14. Known to be human immunodeficiency virus (HIV) positive.
15. History of drug or alcohol dependency or abuse within the 12 months before Screening, or those who have a positive drug test or alcohol test at Screening.

16. Concomitant use of cannabinoids.
17. Inability to follow restriction on watching television, or use of any device with an animated screen (ie, computer, video games, tablets) 24 hours before dosing.
18. A history of prolonged QT syndrome or risk factors for torsade de pointes (eg, heart failure, hypokalemia, family history of long QT Syndrome), or the use of concomitant medications that prolonged the QT/corrected QT (QTc) interval; or prolonged QT/QTc interval (QTc >450 msec) demonstrated on ECG at Screening or Baseline (based on average of triplicate ECGs).
19. Any suicidal ideation with intent with or without a plan within 6 months before Screening or during Screening (ie, answering "Yes" to questions 4 or 5 on the Suicidal Ideation section of the C-SSRS).
20. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS).
21. Any psychotic disorder(s) or unstable recurrent affective disorder(s) evident by use of antipsychotics or prior suicide attempt(s) within approximately the last 2 years.
22. Currently enrolled in another clinical study or used any investigational drug or device within 30 days or 5 half-lives, whichever is longer, preceding informed consent, except the investigational study for the evaluation of commercial IPS machine.
23. Frequent spontaneous background burst or current evidence of proconvulsive activity on EEG (eg, increase in spike-wave activity) at Screening.

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.

9.3.3.1 Study-Specific Withdrawal Criteria

The investigator will determine continued subject participation in the IPS assessments. In individual situations, safety assessments will be completed as appropriate, determined by the investigator.

A subject may be withdrawn from the study if any of the following circumstances occur:

1. If a subject experiences a generalized tonic-clonic seizure on any study day, and the subject has not had a generalized tonic-clonic seizure in the 6 months prior to enrollment, that subject will be discontinued from the study.

OR

1. If a subject experiences a generalized tonic-clonic seizure during IPS, that subject will be discontinued from the study.
2. If, in the opinion of the investigator, a subject has evidence of proconvulsive activity on the EEG (eg, increase in spike-wave activity), following administration of the study drug.

3. If a subject has widening of the photosensitivity range by more than 3 points on 2 consecutive occasions after dosing as compared to Screening, the IPS will be terminated and the subject will not be permitted to participate in further testing on the same day.

Generalized spike and wave discharges greater than 5 seconds defined by absence seizures or isolated myoclonic jerks do not require stoppage of study drug or subject withdrawal.

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

E2730 is the test drug and will be supplied as active pharmaceutical ingredient in capsule at dose strengths of 40 mg and 80 mg. Study site personnel will administer capsules containing E2730 or matched placebo (Table 2) as single oral doses according to the study design. Filled capsules will be packed, labelled, and shipped by the contract manufacturer to each site.

Each subject will receive a single oral dose in a cross-over sequence according to his/her randomization code (Table 3). The following treatments will be administered as a single dose to subjects.

- E2730 40 mg: 1 E2730 40 mg capsule and 1 E2730-matched placebo capsule
- E2730 120 mg: 1 E2730 80 mg capsule and 1 E2730 40 mg capsule
- Placebo: 2 E2730-matched placebo capsules

Table 2 Treatments Administered

Treatment	Study Drug Administered
A	Placebo
B	E2730 40 mg
C	E2730 120 mg

Table 3 Treatment Sequences

Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3
1: ABC	Placebo	E2730 40 mg	E2730 120 mg
2: BCA	E2730 40 mg	E2730 120 mg	Placebo
3: CAB	E2730 120 mg	Placebo	E2730 40 mg
4: ACB	Placebo	E2730 120 mg	E2730 40 mg
5: BAC	E2730 40 mg	Placebo	E2730 120 mg
6: CBA	E2730 120 mg	E2730 40 mg	Placebo

A = Placebo; B = E2730 40 mg; C = E2730 120 mg

9.4.2 Identity of Investigational Product(s)

E2730 will be supplied in powder form as the free base.

9.4.2.1 Chemical Name, Structural Formula of E2730

- Test drug code: E2730

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[redacted]

9.4.2.2 Comparator Drug

Placebo capsule matched to E2730 capsule will be administered.

9.4.2.3 Labeling for Study Drug

E2730 will be labeled in accordance with text that is in full regulatory compliance.

9.4.2.4 Storage Conditions

E2730 will be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that E2730 is maintained within 2ºC to 8ºC. 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 all 3 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.

9.4.4 Selection of Doses in the Study

E2730 is currently studied in the SAD study (Study 002). In rat amygdala kindling model, which is considered the most clinically relevant animal model for investigating the effect of compound on partial-onset seizures, E2730 showed a significant and dose-dependent antiseizure effect after the single oral administration.

Two doses are currently being considered for this study. Based on the data from the ongoing Study 002, the anticipated exposure at the dose of 120 mg will be within the exposure limits imposed by the FDA. An additional, lower dose of 40 mg is being considered to provide exposure data to further evaluate PK/PD relationship of E2730. The data from this study will also support initial dose response analysis and provide a dose for future studies.

The doses in this study will be finalized after all cohorts in Study 002 have been evaluated.

9.4.5 Selection and Timing of Dose for Each Subject

Following an overnight fast of at least 8 hours, subjects will be administered the study drug product with approximately 240 mL (8 fluid ounces) of water on the day of each Treatment Visit (ie, Day 1, Day 22, and Day 43). A light snack can be provided at 30 minutes predose (after clinical laboratory blood collection) and at 2 hours postdose.

9.4.6 Blinding

During the Prerandomization and Randomization Phases, central EEG reading will be performed in a blinded and independent manner. Investigator(s) may consult with the central read only during the Prerandomization Phase, if needed, for EEG-IPS eligibility determination.

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel (with the exception of the pharmacist preparing and dispensing the study drug), and sponsor staff will be blinded to the treatment codes. Randomization code 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.

The E2730 drug substance and placebo will be provided to an unblinded pharmacist in an open-label manner. The unblinded pharmacist will be responsible for preparing and dispensing study drug capsules in accordance with subject randomization in a blinded manner. A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the sponsor. In addition, master code breaker reports or envelopes identifying the treatment group of each subject number will be provided to the site and to the sponsor in sealed envelopes. These code breaker reports or envelopes are not to be opened unless an emergency occurs and knowledge of the subject's randomization code may affect his/her medical treatment. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. The investigator is to record the date and time of opening the code breaker report or envelope and the reason for breaking the code. At the conclusion of the study, where possible, all unused drug supplies at the site, together with master code breaker reports or envelopes, are to be returned to the clinical supply vendor for final reconciliation and disposition.

Data from any completed cohort may be unblinded for review by the sponsor.

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) will be recorded on the Prior & Concomitant Medication CRF or Non-Pharmacological Procedures CRF. Up to 3 concomitant AEDs (Appendix 2) are allowed during the course of the study, provided that the dosage of concomitant AED(s) has remained stable for at least 4 weeks prior to screening. During the study, changes to concomitant AEDs (including dosage) are not permitted.

The investigator will record on the AE CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

9.4.7.1 Prohibited Concomitant Therapies and Drugs

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9.4.7.2 Restrictions During the Study Period

Study drug will be administered on the day of each Treatment Visit (ie, Day 1, Day 22, and Day 43) after an overnight fast of at least 8 hours. Treatments will be administered orally with approximately 240 mL (8 fluid ounces) of water. A light snack can be provided at 30 minutes predose (after clinical laboratory blood collection) and at 2 hours postdose.

Water will be allowed as desired except from the time of dosing until 1 hour after study drug administration.

Subjects will be required to abstain from watching television or using any device with an animated screen (ie, computer, video games, tablets) within the 24 hour period prior to each dosing. Subjects will be required to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period prior to each treatment day.

9.4.8 Treatment Compliance

Not applicable as study drug will be administered in the study site by study personnel and records will be maintained.

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

- 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
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license
- A signed and dated clinical studies agreement

The investigator and the study staff will be responsible for the accountability of all study drugs (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 study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs 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 study drugs 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 (eg, FDA). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and, together with unused study drugs 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 study drugs and containers at the site. Destruction at the site will only occur under circumstances

where regulation or supply type prohibits the return of study drugs 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, study drugs 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, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are 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 site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

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

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History and Epilepsy Medical History

In addition to standard medical history, surgical, and epilepsy history and current medical conditions will be recorded at the Screening Visit. All medical, surgical, and epilepsy history within 10 years must be noted in the Medical History and Current Medical Conditions CRF.

9.5.1.2.2 Height Measurement and BMI computation

Height (cm) will be recorded at the Screening Visit and BMI (kg/m^2) will be computed from height and weight data at screening.

9.5.1.2.3 Urine Drug Test

A 30-mL urine sample will be collected at designated time points as specified in the Schedule of Procedures/Assessments (Table 5). This sample will be tested for common drugs of use/abuse: eg, ethyl alcohol, cocaine, cannabinoids, phencyclidine, opioids (as a group), benzodiazepines, barbiturates, and amphetamines.

9.5.1.2.4 Serology

A 6 mL sample of blood will be taken for hepatitis B surface antigen and hepatitis C antibodies at Screening.

9.5.1.3 Efficacy Assessments

Not applicable

9.5.1.4 Pharmacokinetic, Pharmacodynamic, CCI [redacted] Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples for determination of plasma concentrations of E2730 and its metabolite, M1, will be collected from each subject. PK sampling for plasma concentration will be collected at predose and postdose at 1, 2, 4, 6, and 8 hours on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4). In case of early discontinuation, a PK sample will be taken. Plasma concentrations of E2730 and M1 will be measured using validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) methods.

Information on the PK sample collection, handling, and shipping procedures will be provided to the clinical site either as a stand-alone PK laboratory manual or as part of the (central) Laboratory Manual.

9.5.1.4.2 PHARMACODYNAMIC, CCI [redacted] ASSESSMENTS

All PD assessments will be performed within ±15 minutes of the scheduled time point.

EEG-IPS

PD activity of E2730 will be assessed by suppression of PPR following IPS under 3 conditions (eye closure, eye closed, eye open) using the Grass PS 33 photic stimulator with an unpatterned glass lamp and an intensity of 100cd/m^2/flash at 30 minutes to 2 hours predose, and at 1, 2, 4, 6, and 8 hours postdose. The time course (30 minutes to 2 hours predose to 8 hours postdose) will help assess the onset, maximum change, and duration of the reduction in PPR response. PPR is expected to be within the range, from 2 Hz to 60 Hz, depending on subject sensitivity to IPS.

Standard 19-21-channel EEG equipment will be used for recording including video monitoring and precise recording of duration and frequency of the flashes (sensor or connection with the photostimulator). The international 10-20 system will be used, with 2 additional channels, 1 for eye-movements (to detect changes in eye-condition more easily) and 1 for flash frequencies. A 19-21-channel recording system will be used with a bipolar derivation with emphasis on the parieto-temporal-occipital area (maximum and spreading of EA). The display montage will include T4-T6-O2-O1-T5-T3 and T4-P4-Pz-P3-T3, apart from 2x4 (8) frontal to occipital leads.

The following settings will be used:

- Amplification: 7-10 microV/mm
- High Frequency Filter: 35-70 Hz
- Time constant: 0.3-0.6 sec

- Display speed: 30 mm/sec

Bond and Lader Visual Analogue Scale

The Bond and Lader visual analogue scale (VAS) for CNS–related sedation effects will be measured for each subject at predose, 1, 2, 4, 6, and 8 hours postdose on Day 1 (Visit 2), Day 22 (Visit 3), and Day 43 (Visit 4).

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9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs; laboratory evaluation for hematology, blood chemistry, and urine values; measurement of vital signs and ECGs; and the performance of neurological and physical examinations as detailed in Table 5.

An assessment of suicidality using the C-SSRS will be performed as detailed in Table 5.

9.5.1.5.1 Adverse Events and Events Associated with Special Situations

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 E2730.

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
- 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 at 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 observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit in the Randomization Phase and for 5× the half-life of E2730 (mean terminal elimination phase half-life following a single administration of 20 mg E2730 was 71.2 hours in Study 001). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. Serious adverse events (SAEs) must be collected through the last visit in the Randomization Phase and for 5× the half-life of E2730 (mean terminal elimination phase half-life following a single administration of 20 mg E2730 was 71.2 hours in Study 001)..

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 AE CRF.

Abnormal ECG (QTc) 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 interval is greater than 450 msec and there is an increase of more than 60 msec from baseline. 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 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 (see Section 9.5.1.5.8 for a description of the C-SSRS).

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 9.5.1.5.2 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.

9.5.1.5.2 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.

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 (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

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 5) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 4 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	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, calcium, 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.

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 9.5.1.5.1 and the CRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the AE CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [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 5) by a validated method. BP and pulse will be measured after the subject has been supine for 10 minutes. Triplicate reading of supine vital signs will be measured at all visits except for Screening. All BP measurements should be performed on the same arm, preferably by the same person.

At Screening and during Visit 2, Visit 3, and Visit 4, after supine measurements are completed, subjects will be asked to stand up for 2 minutes, and BP and pulse will be taken in the standing position.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed before drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

At time points when vital signs, ECGs, and blood sampling are performed concurrently, procedures will be performed in the following order: ECGs, vital signs, and then blood sampling. Subjects will rest in the supine position for 10 minutes before and 5 minutes after ECG recordings followed by recording of vital signs in the supine position and in standing position (BP and pulse only), and lastly blood sampling.

9.5.1.5.5 PHYSICAL EXAMINATIONS

Comprehensive and abbreviated physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 5). 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 AE CRF.

Comprehensive Physical Examination

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, skin, and neurological examination. The subject will be queried regarding physical status and subjective symptoms as well. A urogenital examination will only be required in the presence of clinical symptoms related to this region.

Abbreviated Physical Examination

Health status will be assessed by brief evaluation of the head, eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination.

9.5.1.5.6 NEUROLOGICAL EXAMINATIONS

Comprehensive and abbreviated neurological examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 5). Documentation of the neurological 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 neurological examination findings that meet the definition of an AE will be recorded on the AE CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

Electrocardiograms (12-lead) will be obtained as designated in the Schedule of Procedures/Assessments (Table 5).

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AE CRF.

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

C-SSRS

An assessment of suicidality using the C-SSRS will be performed at Screening, postdose at the end of every treatment visit, and at the Follow-up/Early discontinuation visit, as designated in the Schedule of Procedures/Assessments (Table 5).

Pregnancy Test

A serum β-hCG or hCG test will be performed for all women of childbearing potential. A 6-mL sample of blood will be taken at designated time points as specified in the Schedule of Procedures/Assessments (Table 5).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 5 presents the schedule of procedures/assessments for the study.

Table 5 Schedule of Procedures/Assessments in Study E2730-A001-201

Phase	Prerandomization	Randomization				
Period	Screening	Treatment Period 1	Treatment Period 2	Treatment Period 3	Follow-up /Early Discontinuation[a]	Unscheduled
Visit	**1**	**2**	**3**	**4**	**5**	
Study Day	**-21 to -1**	**1**	**22±3**	**43±3**	**64±3**	
Procedures/Assessments						
Informed Consent	X					
Demography	X					
Randomization		X				
Inclusion/exclusion criteria	X	X				
Medical history	X					
Epilepsy medical history	X					
Physical examination[b]	X	X			X	
Neurological examination[b]	X	X	X	X	X	
Vital signs[c]	X	X	X	X	X	X
Height and weight[d]	X	X			X	
12-Lead ECG[e]	X	X	X	X	X	X[f]
Clinical laboratory tests[g]	X	X	X	X	X	X
Urine drug test	X					
Urine pregnancy test[h]		X	X	X	X	
Serum β-hCG [or hCG] test[h]	X					
Serology (HCVAb, HBsAg)	X					
PK sampling (plasma)[i]		X	X	X	X	

Table 5 Schedule of Procedures/Assessments in Study E2730-A001-201

Phase	Prerandomization	Randomization				
Period	**Screening**	**Treatment Period 1**	**Treatment Period 2**	**Treatment Period 3**	**Follow-up /Early Discontinuation[a]**	**Unscheduled**
Visit	**1**	**2**	**3**	**4**	**5**	
Study Day	**-21 to -1**	**1**	**22±3**	**43±3**	**64±3**	
Procedures/Assessments						
CCI		X				
C-SSRS	X	X	X	X	X	
EEG-IPS Assessment[k]	X[l]	X[m]	X[l]	X[l]		
Bond and Lader VAS[k,n]		X	X	X		
Administer study drug		X	X	X		
Prior and concomitant medication(s)	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X

ß-hCG = beta-human chorionic gonadotropin *(*or hCG = human chorionic gonadotropin*)*, BP = blood pressure, C-SSRS = Columbia-Suicide Severity Rating Scale, EEG-IPS= electroencephalogram- intermittent photic stimulation, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, CCI
PK = pharmacokinetics, QTc = corrected QT interval, VAS = visual analogue scale.

a: To be completed for all subjects, including those who discontinue the study early.

b: A full physical examination will be carried out at Screening. A brief physical examination may be carried out at other visits, as deemed necessary by the investigator. A neurological examination will be performed at screening, at each treatment visit (predose and at 4 hours postdose), and during the Follow up/Early Discontinuation visit (as applicable). Clinically significant abnormal findings from the physical or the neurological examinations will be reported as AEs.

c: Vital signs measurements will be taken at screening. In addition, on each dosing day, vital sign (BP, pulse, body temperature, respiratory rate) measurements will be obtained at predose, 1, 2, 4, 6, and 8 hours postdose. Subjects will need to rest for 10 minutes before vital signs are taken in the supine position. Triplicate reading of supine vital signs will be measured at all visits except for Screening. At Screening and during the Treatment periods, after supine measurements are completed, subjects will be asked to stand up for 2 minutes, and BP and pulse will be taken in the standing position. At time points when vital signs, ECGs, and blood sampling are performed concurrently, procedures will be performed in the following order: ECGs, vital signs, and then blood sampling. Subjects will rest in the supine position for 10 minutes before and 5 minutes after ECG recordings followed

Table 5 Schedule of Procedures/Assessments in Study E2730-A001-201

Phase	Prerandomization	Randomization				
Period	Screening	Treatment Period 1	Treatment Period 2	Treatment Period 3	Follow-up /Early Discontinuation[a]	Unscheduled
Visit	1	2	3	4	5	
Study Day	-21 to -1	1	22±3	43±3	64±3	
Procedures/Assessments						

by recording of vital signs in the supine position and in standing position (BP and pulse only), and lastly blood sampling.

d: At Screening, both height and weight will be measured. At all other visits, only weight will be measured.

e: ECG assessments will be performed in the supine position at predose and 4 hours postdose (on each dosing day). If during any visit the QTc was measured as >450 msec, 3 consecutive ECGs separated by 5 – 10 minutes will be performed to confirm the abnormality.

f: During the unscheduled visits, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.

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

h: Female subjects of childbearing potential only.

i: Blood samples for plasma PK will be obtained at predose and postdose at 1, 2, 4, 6, and 8 hours on Days 1, 22, and 43. In case of early discontinuation, a PK sample will be taken.

j: CCI [redacted]

k: All PD assessments will be performed within ±15 minutes of the scheduled time point.

l: EEG-IPS assessment will be performed at 5 time points, over an approximately 4-hour time period (0, 1, 2, 3, and 4 hours).

m: EEG-IPS assessment will be performed 30 minutes to 2 hours predose and repeated at approximately 1, 2, 4, 6, and 8 hours postdose on Days 1, 22, and 43.

n: The Bond and Lader VAS for CNS–related sedation side effects will be measured from each subject at predose, 1, 2, 4, 6, and 8 hours postdose on Days 1, 22, and 43.

Table 6 presents the blood sampling schedule for pharmacokinetic assessments. In case of early discontinuation, a PK sample will be taken.

Table 6 Blood Sampling Schedule for Pharmacokinetic Assessments

Days	Time Relative to the Administration	Acceptable Time Window
Day 1 (Visit 2), Day 22 (Visit 3) (±3 days), Day 43 (Visit 4) (±3 days)	Predose	–2 hours
	1 and 2 hours	±5 minutes
	4, 6, and 8 hours	±15 minutes

9.5.2.2 Description of Procedures/Assessments Schedule

The scheduling of study procedures and assessments is shown in Table 5.

9.5.3 Appropriateness of Measurements

Most of the clinical assessments are standard measurements commonly used in Phase 2 studies of epilepsy. The safety assessments to be performed in this study, including monitoring and recording all AEs; laboratory evaluation for hematology, blood chemistry, and urine values; measurement of vital signs and ECGs; and the performance of neurological and physical examinations, are standard evaluations to ensure subject safety.

In addition to the standard safety measurements, Bond and Lader VAS will be conducted in this study. The Bond and Lader VAS (Bond, 1974) is a sensitive tool to assess CNS side effects (somnolence, body sway, dizziness and sedation etc.). Since CNS related side effects were observed in nonclinical studies of E2730, Bond and Lader VAS is included for assessment of CNS-related sedation effects in this study.

The EEG-IPS procedure during this study will be performed based upon the protocol of Kastelejin et al (Kastelejin-Nolst Trenité, et al, 1996). The combination of lower and upper frequencies gives a total of 3 photosensitivity ranges, 1 per eye condition (eye closure, eyes closed, and eyes open). In order to minimize the risk of inducing a seizure, photic stimulation will not be carried out between the upper and lower thresholds. However, qualified medical personnel for the management of acute seizures will be present during the day of EEG-IPS procedure throughout the duration of the study.

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 1 business day from the date the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the last visit in the Randomization Phase and for 5× the half-life of E2730 (mean terminal elimination phase half-life following a single administration of 20 mg E2730 was 71.2 hours in Study 001). 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.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

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 IRB of the occurrence of the SAE in writing, if required by his institution. A copy of this communication must be forwarded to the CRO 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 which the estimated date of conception is either before the last visit or within 28 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, an induced abortion, or a spontaneous abortion 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 1 business day 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 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

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 AE 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 is 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 AE CRF.

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

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. 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 ED procedures indicated in the Schedule of Procedures/Assessments (Table 5).

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, withdrawal of consent, 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.

A subject removed from the study for any reason may be replaced.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

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 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.

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. Statistical analyses will be performed using SAS software or other validated statistical software as required.

Descriptive statistics will be presented including mean and standard deviation of photosensitivity range for each subject at Screening and at each time point, for each Treatment visit day by treatment group. Graphical displays of the data for each subject will allow exploration of intersubject and intrasubject variability. Details of statistical methods and analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of 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

The reduction in PPR response will be evaluated for 8 hours postdose for the entire time period. A diminution in response is anticipated with the dose range. A statistical difference of treatment doses versus placebo will be evaluated.

The primary endpoint, the change in the PPR range, is evaluated using mixed effects model for comparing low and high treatment doses versus placebo. Another endpoint will include proportions of subjects responding to treatment versus placebo. Most patients have strong responses to effective treatments compared to placebo, which can be evaluated by graphs of partial response (ie, 3 steps narrowing) and abolition of PPR.

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of this study is the mean change from baseline in the PPR range in each subject's most sensitive eye condition at each dose level of E2730 as compared to placebo.

9.7.1.1.2 SECONDARY ENDPOINTS

- Mean changes from baseline in PPR ranges in each subject's eye closure, eyes closed, and eyes open condition at each dose level of E2730 as compared to placebo
- Onset, maximum change, and duration of photosensitivity response at each dose level in all 3 eye conditions at the time course of E2730 as compared to placebo
- Frequency and percentage of subjects with Complete Suppression, Partial Response, and no Response of PPR at each dose level of E2730 as compared to placebo
- Occurrence of AEs or changes in the neurological examination after single doses of E2730 compared to placebo
- Changes in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2730 compared to placebo
- PK of E2730 and its N-acetyl metabolite, M1
- Relationship between PK parameters of E2730 onset, maximum change, and duration of impact on photosensitivity

9.7.1.2 Definitions of Analysis Sets

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

The Pharmacokinetic Analysis Set is the group of randomized subjects who receive at least 1 dose of study drug and have sufficient PK data to derive at least 1 PK parameter.

The Pharmacodynamic Analysis Set is the group of randomized subjects who receive at least 1 dose of study drug and have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened and the number failing screening (overall and by reason for failure) will be summarized. Screen failure data will be listed. The number of subjects randomized along with the number of subjects administered each dose of E2730 will also be presented.

Subjects who prematurely terminate their participation in the study will be summarized by their primary reason for study termination.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized by dose group for each part of the study using descriptive statistics. Continuous demographic and baseline variables include age, height, and weight; categorical variables include sex, age group, 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 by treatment group, Anatomical Therapeutic Chemical (ATC) class, and World Health Organization Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the dose of study drug. Concomitant medications will be defined as medications that started after the date of the dose of study drug up to 28 days after the subject's dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

Not applicable.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, CCI Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The PK Analysis Set will be used for listings of individual E2730 and M1 plasma concentrations, summaries and listings of PK parameters. Plasma concentrations will be tabulated by nominal sampling time and summarized by treatment dose using summary statistics.

The following PK parameters will be derived by noncompartmental analysis using plasma concentrations of E2730 and M1. These parameters will include, but are not limited to:

- C_{max} maximum observed concentration
- $AUC_{(0-8h)}$ area under concentration x time curve from time 0 to 8 hours postdose
- t_{max} time to reach C_{max} following drug administration

The PK of E2730 will be analyzed based on available data from this study. The PK and PD Analysis datasets will be used to evaluate the relationship of PK of E2730 and change in PPR response. The PK-PD analyses may include the examination of the relationship of PK of E2730 and PPR response (eg, time of onset, maximum change, and duration of PPR; Bond and Lader data) using model-based approaches.

Analysis variables: Plasma concentrations of E2730 and *N*-acetyl metabolite (M1)

Analysis set: The Pharmacokinetic Analysis Set will be used for individual plasma concentration listings and summaries of plasma concentrations.

Analysis methods: The PK of E2730 will be analyzed based on available data from this study. Plasma concentrations will be tabulated by nominal sampling time and summarized by treatment dose using summary statistics.

9.7.1.7.2 PHARMACODYNAMIC, CCI [redacted] ANALYSES

The PD analysis will be performed on the PD Analysis Set.

No multiplicity adjustments will be made. The 5 PPR measured postdose on a study day will be averaged and used for the primary endpoint. The predose PPR data from the respective treatment period will be used as the baseline data.

The primary and secondary endpoints of mean change from baseline of the average PPR for each E2730 dose compared with placebo in the most sensitive and different eye conditions will be performed using a mixed effects model for crossover study. The model will include treatment, period, and sequence as fixed effects, baseline (predose) measurement as a covariate, and subject nested within sequence as a random effect. Where data are normally distributed, least squares (LS) means, difference in LS means of each E2730 dose compared to placebo, and 90% CIs will be presented with no adjustments for multiplicity.

Additional analysis by graphical exploration on onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions at the time course of E2730 as compared to placebo. This analysis will provide further information on the frequency and percentage of subjects with Complete Suppression, Partial Response, and No Response of PPR at each dose level of E2730 as compared to placebo.

Sensitivity analyses for PPR may be conducted, for example, of PPR for subjects who completed Treatment Periods 1-3 versus those who are included in the PD Analysis Set. CCI [redacted] All PD data (Bond and Lader) will be listed and summarized by treatment, as appropriate, using standard summary statistics. Descriptive summary statistics (eg, mean, SD, median, minimum, and maximum

for continuous variables, and the number and percent for categorical variables) of each endpoint and the changes from baseline will be tabulated.

CCI [redacted]

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and neurological/physical examinations. Treatment-emergent adverse events (TEAEs) will be summarized by presenting for each treatment group, the incidence of AEs.

An assessment of suicidal ideation and behavior using the C-SSRS will be performed throughout the study.

Descriptive summary statistics (eg, mean, SD, median, minimum, and maximum for continuous variables, and the number and percent for categorical variables) of the laboratory, vital signs, and ECG parameters, and changes from baseline will be evaluated by treatment group. The proportion of subjects with any treatment-emergent report of suicidal ideation and behavior and intensity of these behaviors will be summarized.

9.7.1.8.1 Extent of Exposure

Extent of exposure will be presented by dose level.

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 20.0 or higher) lower level term (LLT) 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, using the Safety Analysis Set. 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]). A subject data listing of all SAEs, including deaths, will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, 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 Section 9.5.1.5.3 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 also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) 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 was 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 may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

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

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia during the treatment period will be summarized. Clinically abnormal ECG results in QTc Fridericia will be categorized as follows:

- For the QT interval assessment, clinically abnormal ECG results for QT interval corrected for heart rate using Fridericia's formula (QTcF) will be categorized as follows: QTcF values >450 msec, >480 msec, and >500 msec, and time-matched change from baseline in QTcF >30 msec and >60 msec.

9.7.1.8.6 OTHER SAFETY ANALYSES

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

9.7.2 Determination of Sample Size

Approximately 9 subjects with photosensitive epilepsy and a stable PPR will be needed to be randomized in the study in order to obtain 6 evaluable subjects. Based on a similar study in subjects with photosensitive epilepsy (NCT02564029), an estimated standard deviation of the treatment group difference of the SPR in the subject's most sensitive eye condition is 3.62. The width of a 90% CI of the mean group difference based on this standard deviation assumption and 6 subjects is 2.431. Therefore, a sample size of 6 would be sufficient to detect a mean group difference of 3 or larger with 90% confidence.

9.7.3 Interim Analysis

No formal 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.

10 REFERENCE LIST

CCI

Bond A, Lader M. The use of analogue scales in rating subjective feelings. Br. J. med. Psychol. 1974; 47: 211-8.

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Kasteleijn-Nolst Trenité DG, Marescaux C, Stodieck S, Edelbroek PM, Oosting J. Photosensitive epilepsy: a model to study the effects of antiepileptic drugs. Evaluation of the piracetam analogue, levetiracetam. Epilepsy Res. 1996;25:225-30.

Löscher W, Luna-Tortós C, Römermann K, Fedrowitz M. Do ATP-binding cassette transporters cause pharmacoresistance in epilepsy? Problems and approaches in determining which antiepileptic drugs are affected. Curr Pharm Des. 2011;17(26):2808-28.

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Columbia-Suicide Severity Rating Scale (C-SSRS). Columbia University. Available from: http://www.cssrs.columbia.edu/scales_cssrs.html

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 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 and the Competent Authorities 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 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 interactive response system, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, 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 correction 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.

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 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an

ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

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 drugs 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, or upon notification of the sponsor, 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 – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
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×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L 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	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<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 – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 Prohibited Concomitant Medications

Prohibited Concomitant Medication		
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The above list of prohibited concomitant medications is not exhaustive.

The investigator should provide further guidance before switching any of the concomitant medications mentioned in the above list.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2730-A001-201

Study Protocol Title: A Multicenter, Double-Blind, Randomized, Cross-Over Study Evaluating Pharmacodynamic Activity of E2730 in Adult Subjects with Photosensitive Epilepsy

Investigational Product Name: E2730

IND Number: 124728

SIGNATURES

Authors:

PPD

Eisai, Inc. Date

PPD

Eisai, Inc. Date

PPD

Eisai, Inc. Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2730-A001-201
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Cross-Over Study Evaluating Pharmacodynamic Activity of E2730 in Adult Subjects with Photosensitive Epilepsy
Investigational Product Name:	E2730
IND Number:	124728

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.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date