16.1.1 Protocol and Protocol Amendments

The following versions of the protocol are provided

- E2082-A001-201 V2.0_12 Apr 2019
- E2082-A001-201 V1.0_21 Aug 2018

REVISION HISTORY

Revisions to Version 1.0 (per Amendment 01) **Amended version/Date: v2.0, 12 Apr 2019**		
Change	**Rationale**	**Affected Protocol Sections**
Included E2082 10 mg dose to the open-label treatment, and the following changes/inclusions are made to the study design accordingly: • For newly enrolled or ongoing subjects in the study who have completed up to the Treatment Period 3 at the time of Protocol Amendment 01 implementation, the dose to be administered during the Treatment Period 4 will be provided by an independent unblinded biostatistician upon review of the subject's PPR data collected during Treatment Periods 1 through 3. • Modified the study design to allow subjects who completed the study before the protocol Amendment 01 to re-enter the study to receive E2082 10-mg open-label treatment. • Added additional study visits and new schedule of assessments table for subjects in Scenario 3 • Updated study visits throughout the protocol per the changes made to the study design and schedule of assessments	In addition to 25 mg in the Original Protocol version, 10 mg is being added in Protocol Amendment 01 in order to better characterize dose/exposure-response relationship and to support dose recommendation for Phase 2 and 3 clinical studies in target patient population.	**Synopsis** - Study design, Study treatments, Inclusion Criteria, Assessments • Section 9.1 • Section 9.1.1.1 • Section 9.1.2.2 • Section 9.4.1.2 • Section 9.4.4 • Section 9.4.5 • Section 9.4.6 • Section 9.4.7.2 • Section 9.5.1.2.3 • Section 9.5.1.4.1 • Section 9.5.1.4.1 • Section 9.5.1.5.8 • Section 9.5.2.1
Modified the Inclusion Criterion No. 3: Modified the text "up to a maximum of 3 concomitant antiepileptic drugs (AEDs) are allowed provided that doses must have remained stable for at least 4 weeks before Screening. In the case where a new AED regimen has been initiated for a subject, the dose must be stable for at least 8 weeks before Screening." to "up to a maximum of 3 concomitant AEDs are allowed provided that doses must have remained stable for at least 4 weeks or 5 half-lives, whichever longer, before Screening. In the case where a new AED regimen has been initiated for a subject, the subject must be on the new AED for at least 8 weeks and the dose must have remained stable for at least 4 weeks or 5 half-lives, whichever is longer, before Screening." The text in the Prior and Concomitant Therapy section is updated appropriately in consistent with the Changes in Inclusion Criterion No. 3.	Correction for clarity	**Synopsis** Inclusion Criteria, Concomitant Drug/Therapy • Section 9.1.2 • Section 9.3.1 • Section 9.4.7

Added the text "consumption of dietary supplements, foods, and forms of fruit juice that may affect the expression or function of cytochrome P450 (CYP)3A within 14 days before study drug administration" to the Exclusion Criterion No. 21' and also updated the Prohibited Concomitant Therapies and Drugs section accordingly.	Correction for clarity	**Synopsis** Exclusion criteria Concomitant drug/Therapy • Section 9.3.2 • Section 9.4.7.1
Modified inclusionary age range from "18 to 60 years" to "18 to 65 years" (see Inclusion Criterion No. 1).	To increase upper age limit allowed in this study.	**Synopsis** Inclusion criteria • Section 9.3.1
Added a note "Subjects who have completed the study per original protocol may re-enter the study provided that the subject meet inclusion criteria No. 2 to 7" in the inclusion criteria. Added a note "Subjects in Scenario 3 will not be allowed to re-enter the study if they meet any of the exclusion criteria listed above" in the exclusion criteria	To improve clarity	**Synopsis** Inclusion criteria Exclusion criteria • Section 9.3.1 • Section 9.3.2
Specified the timing of study unblinding for planned data analyses – (1) first analysis to take place when all subjects completed the double-blind, randomized crossover treatment period, and (2) second (final) analysis to take place at study completion.	To improve clarity	• Section 9.7

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2082-A001-201
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Crossover, Single-Dose Study with An Open-Label Treatment Period Evaluating Pharmacodynamic Activity of E2082 in Adult Subjects with Photosensitive Epilepsy
Sponsor:	Eisai Inc. 100 Tice Boulevard, Woodcliff Lake, New Jersey 07677, US
Investigational Product Name:	E2082
Indication:	Not applicable
Phase:	2
Approval Date:	V1.0 21 Aug 2018 (original protocol) V2.0 12 Apr 2019 (Protocol Amendment 01)
IND Number:	134556
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.: E2082

Name of Active Ingredient: 2-Fluoro-6-[3-fluoro-8-oxo-7-(pyridin-3-yl)-7,8-dihydro-6*H*-pyrano[3,2-*b*:5,4-*b'*]dipyridin-9-yl]benzonitrile

Study Protocol Title

A Multicenter, Double-Blind, Randomized, Crossover, Single-Dose Study with An Open-Label Treatment Period Evaluating Pharmacodynamic Activity of E2082 in Adult Subjects with Photosensitive Epilepsy

Principal Investigator

Gregory Krauss, MD

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 8 to 9 months.

Phase 2

Objectives

Primary Objective

- To assess pharmacodynamic (PD) activity of E2082 as measured by suppression of epileptic photoparoxysmal response (PPR) in the subject's most sensitive eye condition in the photosensitivity model as a proof of principle of efficacy in subjects with photosensitive epilepsy, compared to placebo

Secondary Objectives

- To assess the PD activity of E2082 as measured by suppression of PPR in each of the 3 eye conditions (eye closure, eyes closed, and eyes open), compared to placebo
- To assess PD activity of E2082 as measured by onset, maximum change, and duration of photosensitivity response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- To assess proportion of subjects with complete suppression, partial suppression, and no response of standardized photosensitivity response (SPR)
- To assess other central nervous system (CNS)-related effects of E2082 based on Bond-Lader Visual Analogue Scale (BL-VAS)
- To assess the safety and tolerability of E2082 following single oral dose administration
- To assess the pharmacokinetics (PK) of E2082 following single oral dose administration

Exploratory Objective

- To explore relationships between PK and PD

Study Design

This is a multicenter, double-blind, randomized, 6-sequence, 3-treatment, 3-period, crossover study with an Open-Label Treatment Period, in adult subjects with photosensitive epilepsy. This study will use the photosensitivity proof of principle model to determine the potential of E2082 to reduce the photosensitive range in adult subjects.

This study will have 2 phases: Pretreatment Phase and Treatment Phase. The Pretreatment Phase will consist of a Screening Period (up to 3 weeks from Visit 1), during which each subject's study eligibility will be determined. The Treatment Phase will consist of 3 blinded Treatment Periods for a randomized crossover design, followed by an Open-label Treatment Period. During the Randomized Crossover Treatment Periods, there will be 3 Treatment Visits (Visit 2 [Treatment Period 1], Visit 3 [Treatment Period 2], and Visit 4 [Treatment Period 3]) evaluating single-dose administrations of either placebo, E2082 2.5 mg, or E2082 25 mg in a blinded manner.

Scenario 1: Newly enrolled or ongoing subjects who have completed upto the Treatment Period 3 at the time of Protocol Amendment 01 implementation, will undergo 1 treatment visit (Visit 5 [Treatment Period 4]) during the Open-label treatment period to receive a single-dose administration of E2082 40 mg or 10 mg; the dose to be administered will be provided by an independent unblinded biostatistician upon review of the subject's PPR data collected during Treatment Periods 1 through 3. (revised per Amendment 01)

Scenario 2: Subjects who completed the open-label Treatment Period 4 (Visit 5), and have not completed the Follow-Up visit [Visit 6]) by the time of Protocol Amendment 01 implementation may continue in the study to receive an additional open-label, single oral dose of E2082 10 mg in the Treatment Period 5 (Visit 8) without undergoing Follow-up Visit 1 (Visit 6) and Screening 2 (Visit 7). (revised per Amendment 01)

Scenario 3: Subjects who completed the study (including Follow-Up visit [Visit 6]) before the implementation of Protocol Amendment 01 may be allowed to re-enter the study to receive an open-label, single-dose administration of E2082 10 mg in the Treatment Period 5 after Screening 2 (Visit 7). (revised per Amendment 01)

Treatment visits (ie, Visit 2, Visit 3, Visit 4, and Visit 5) will each be separated by a 2-week (±3 days) washout interval for a total of approximately 6 weeks. Treatment Period 5 (Visit 8) will be 2 weeks (±3 days) after Treatment Period 4 (Visit 5) for subjects in Scenario 2, and after Screening 2 for subjects in Scenario 3. (revised per Amendment 01)

All subjects will undergo a Follow-up Period of 2 weeks (±3 days) after the last day of study product administration (Visit 5 and/or Visit 8, as applicable). (revised per Amendment 01). The anticipated study participation duration for each subject is approximately 11 to 15 weeks (revised per Amendment 01). All visits will be conducted on an outpatient basis.

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 meeting all eligibility criteria will enter into the Treatment Phase and be randomly assigned to 1 of 6 treatment sequences to receive, in a blinded fashion, a single oral dose of placebo control, E2082 2.5 mg, or E2082 25 mg during the Randomized Crossover Treatment Periods. This is followed by the Open-Label Treatment Period, during which each subject will receive a single dose of E2082 40 mg and/or 10 mg. (revised per Amendment 01)

On the day of each Treatment Visit (ie, Visit 2, Visit 3, Visit 4, Visit 5, and, as applicable Visit 8), subjects will arrive at the clinic in the morning following an overnight fast of at least 8 hours. Baseline intermittent photic stimulation (IPS)-electroencephalogram (EEG) assessments will be conducted 30 minutes to 2 hours before study product administration on each treatment day, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency

for each eye condition.

After completion of the Open-label Treatment Period(s), subjects will enter the Follow-up Period, during which they will be required to complete a Follow-up visit (Visit 6 and/or Visit 9, as applicable) at 2 weeks ±3 days following the last day of study product administration.

Subjects who discontinue early from the study for any reason after having been exposed to study drug will undergo an Early Discontinuation Visit within 2 weeks ±3 days of their last dose of study drug. Early Discontinuation visit is not required for subjects who discontinued from the study before receiving the first study drug administration. Upon consultation with the sponsor, subjects who discontinue from the study early may be replaced.

The end of study is defined as the last subject completing the Follow-up Visit.

IPS-EEG specific Subject Withdrawal/Stopping Criteria

At the discretion of the investigator, a subject may be withheld from further IPS-EEG testing during a study visit or withdrawn from the study if any of the following 3 circumstances occur:

1. If a subject experiences:

   a) generalized tonic-clonic seizure (GTCS) on any study day, and the subject has not had a GTCS in the 6 months before enrollment, that subject will be discontinued from the study.

   OR

   b) GTCS during photic stimulation, 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, that subject will be discontinued from the study.
   Proconvulsive activity is defined as:

   a) 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; or

   b) change in the usual pattern of PPR that is typical for the subject such as: decrease in time to occurrence of PPRs at the same flash frequency; increase in the duration of the PPR; or, clear increase of PPR-related negative sensations (clinical signs) or appearance or increase of spontaneous epileptiform activity.
3. If a subject has widening of the photosensitivity range (becomes more sensitive) by more than 3 points on 2 consecutive occasions after dosing compared to Screening, the IPS will be terminated and the subject will not be permitted to participate in further IPS-EEG testing on the same day.

Number of Subjects

Approximately 9 subjects will be randomized to achieve 6 evaluable subjects.

Inclusion Criteria

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

1. Male or female 18 to 65 years of age at the time of informed consent.
2. A diagnosis and/or history of a PPR on EEG (ie, photosensitivity epilepsy).
3. If currently being treated with antiepileptic drugs (AEDs), up to a maximum of 3 concomitant AEDs is allowed provided that doses must have remained stable for at least 4 weeks or 5 half-lives, whichever is longer, before Screening. In the case where a new AED regimen has been initiated for a subject, the subject must be on the new AED for at least 8 weeks, and the dose must have remained stable for at least 4 weeks or 5 half-lives, whichever is longer, before Screening. (See Exclusion Criteria No. 17-22 for AEDs that are

exclusionary)

4. Reproducible IPS-induced PPR on EEG of at least 3 points on the SPR scale in at least 1 eye condition (eye closure, eyes closed, eyes open) on at least 3 of the EEGs performed at Screening.
5. Body mass index (BMI) between 18 to 35 kg/m^2 (inclusive) and a total body weight greater than or equal to 45 kg at Screening.
6. Agrees to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period before each treatment day.
7. Willing and able to comply with all aspects of the protocol.

   Note: Subjects who have completed the study per original protocol may re-enter the study provided that the subject meet inclusion criteria No. 2 to 7.

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 [β-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of β-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 before Screening.
6. Ongoing or history of GTCS within 6 months before Screening.
7. Subject who had developed a clinical seizure during previous PPR assessment, or who experiences a clinical seizure during the Screening IPS procedure.
8. Frequent spontaneous background burst or current evidence of proconvulsive activity on EEG (eg, increase in spike-wave activity) at Screening.
9. Inability to follow restriction on watching television, or use of any device(s) with an animated screen (eg, computer, video games, tablets, or smart phone) from the time of arrival at the study center until study procedures are completed for that day.
10. Currently active 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. 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 using Fridericia formula (QTcF) interval; or prolonged QT/QTcF interval (QTcF >450 msec) demonstrated on ECG at Screening or Baseline (based on average of triplicate ECGs).
12. Presence of 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.
13. Current/ongoing clinically significant active liver disease, porphyria, or with a family history of severe hepatic dysfunction indicated by abnormal liver function tests (LFTs) greater than 3 times the upper limit of normal (ULN) (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).
14. Any history of gastrointestinal conditions or surgery that may affect PK profiles of E2082 (eg, hepatectomy, nephrectomy, and digestive organ resection).
15. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening.
16. Use of perampanel within 6 weeks before Screening.
17. Use of felbamate for less than 2 years or where the dose has not been stable for at least 8 weeks before Visit 1. Subject must not have a history of white blood cell (WBC) count below equal or less than 2500/μL (2.50 1E+09/L), platelet count below 100,000, LFTs above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If subjects received felbamate in the past, it must have been discontinued 8 weeks before Visit 1 to be eligible for study participation.
18. Use of vigabatrin within 5 months before Screening. Subjects who have discontinued vigabatrin for at least 5 months before Screening must have documentation showing no evidence of vigabatrin-associated clinically significant abnormality in a visual perimetry test in order to be eligible for the study.
19. Concomitant use of cannabinoids.
20. Use of benzodiazepines for epilepsy for which the dose has not been stable for greater than 4 weeks before Screening. Benzodiazepine use as rescue medication for seizure control is allowed; however, intermittent use of benzodiazepines for any other indication (eg, anxiety/sleep disorders) is prohibited.
21. Use of concomitant AEDs or other drugs that are known to be potent cytochrome P450 (CYP)3A enzyme inducers (such as carbamazepine, oxcarbazepine, eslicarbazepine,

phenytoin, phenobarbital, and primidone) or CYP3A inhibitors within 4 weeks or 5 half-lives, whichever is longer, before screening. In addition, consumption of dietary supplements, foods, and forms of fruit juice that may affect the expression or function of CYP3A within 14 days before study drug administration. (revised per Amendment 01)

22. Vagus nerve stimulation (VNS) implanted within 5 months or changes in parameter within 4 weeks before Screening.
23. On a ketogenic diet for which the diet is not a stable regimen for at least 4 weeks before Screening.
24. History of drug or alcohol dependency or abuse within the 12 months before Screening, or those subjects who have a positive drug test or alcohol test at Screening.
25. History of or ongoing multiple drug allergies or severe drug reaction to AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
26. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
27. 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 Columbia-Suicide Severity Rating Scale [C-SSRS]).
28. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS).
29. 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.
30. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5 half-lives, whichever is longer, preceding informed consent, except the investigational study for the evaluation of commercial IPS machine.

    Note: Subjects in Scenario 3 will not be allowed to re-enter the study if they meet any of the exclusion criteria listed above.

Study Treatments

Test Drug: E2082

E2082 will be supplied as 0.5-mg and 5-mg tablets for oral administration.

Comparator Drug: E2082-matched placebo

Randomized Crossover Treatment Periods

Each subject will receive a single oral dose of E2082 2.5 mg, E2082 25 mg, and matched-placebo in a cross-over sequence according to his/her randomization code.

Treatment A (Placebo): 5 x E2082-matched placebo tablets
Treatment B (E2082 2.5 mg): 5 x E2082 0.5-mg tablet
Treatment C (E2082 25 mg): 5 x E2082 5-mg tablets

Open-label Treatment Period

Scenario 1: Each subject will receive a single oral dose of E2082 40 mg (8 x E2082 5-mg tablets) or 10 mg (2 x E2082 5-mg tablets). (revised per Amendment 01)

Scenario 2 and 3: Each subject will receive a single oral dose of E2082 10 mg (2 x E2082 5-mg tablets) during Visit 8. (revised per Amendment 01)

All Study Drug 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 approximately 30 minutes predose (after clinical laboratory blood collection) and approximately 2 hours postdose. Water will be permitted ad libitum except from the time of dosing until 1 hour postdose.

Duration of Treatment

Single dose

(ie, the Treatment Phase will consist of 4 or 5 Treatment Periods each with a single dose administration) (revised per Amendment 01)

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 or 5 half-lives, whichever is longer, before Screening. In the case where a new AED regimen has been initiated for a subject, the subject must be on the new AED for at least 8 weeks, and the dose must have remained stable for at least 4 weeks or 5 half-lives, whichever is longer, before screening. During the study, changes to concomitant AEDs (including dosage) are not permitted unless medically necessary and upon consultation with the Sponsor.

Use of the following AEDs during the course of the study is not allowed:

- Perampanel
- Vigabatrin
- Cannabinoids
- Benzodiazepines for non-epilepsy indications (eg, anxiety/sleep disorders)
- Enzyme-inducing antiepileptic drugs (EIAEDs, eg, carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, phenobarbital, and primidone)

Concomitant use of medications known to be potent CYP3A inducers/inhibitors including, but not limited to, rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, modafinil, pioglitazone, and rifabutin will not be permitted and are to be discontinued within 4 weeks or 5 half-lives, whichever is longer, before Visit 1, and as applicable, Visit 7. In addition, as E2082 is predominantly metabolized

by CYP3A, the consumption of dietary supplements, foods, and forms of fruit juice that may affect the expression or function of CYP3A should be avoided 14 days before study drug administration. Examples of such dietary supplements, foods, and forms of fruit juice are grapefruit, grapefruit juice, grapefruit-containing beverages or other products for consumption. (revised per Amendment 01)Vagus nerve stimulation (VNS) is not considered as one of the 3 allowed concomitant AEDs. However, VNS implantation during the course of the study is prohibited. For subjects who have VNS implanted before participation in this study, changes to VNS parameters are not allowed unless medically necessary.

Changes to ketogenic diet (eg, median chain triglyceride level) are not allowed during the study.

Assessments

Efficacy Assessments

Not applicable.

Pharmacokinetic Assessments

On each treatment day, blood samples for the determination of plasma concentrations of E2082 will be collected from each subject predose (within 2 hours), and at 1 (±10 min), 2 (±10 min), 4 (±15 min), 6 (±15 min), and 8 (±15 min) hours postdose.

Pharmacodynamic Assessments

IPS-EEG

PD activity of E2082 will be assessed by suppression of PPR following IPS using the Grass PS 33 photic stimulator with an unpatterned glass lamp and an intensity of 100 cd/m^2/flash. Each IPS-EEG assessment will be conducted in all 3 eye conditions (eye closure, eyes closed, and eyes open; each for a minimum of 2.5 minutes) at ascending and then descending photo stimulation frequencies. The lower and upper limit of photosensitivity to IPS threshold frequency will be determined for each eye condition. PPR is expected to be within the range of 2 Hz to 60 Hz, depending on the subject's sensitivity to IPS. Qualified medical personnel for the management of acute seizures will be present during the day of IPS-EEG procedure throughout the study.

During the Screening Visit (Visit 1, and, as applicable Visit 7) (revised per Amendment 01), IPS-EEG assessment will be performed at 5 time points, over a 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. However, the final determination of study eligibility will include predose assessments when the subject returns to study site for Visit 2. On each treatment day (ie, Visit 2, Visit 3, Visit 4, Visit 5, and as applicable Visit 8) (revised per Amendment 01), IPS-EEG assessments will be conducted predose (approximately 30 minutes to 2 hours), and at 1, 2, 4, 6, and 8 hours (within ±15 minutes of each scheduled time point) postdose to characterize the time course of E2082 PD activity including the onset, maximum change from baseline, and duration of the reduction in PPR response. The predose assessment serves as the baseline on each treatment day.

Other PD assessments

The BL-VAS (Bond A, 1974) for CNS-related effects of E2082 (such as somnolence, sedation, dizziness, and body sway) for potential sedative effects of E2082 will be evaluated for each subject on each treatment day predose (within 2 hours) and at 1, 2, 4, 6, and 8 hour postdose.

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

Pharmacogenomic and Other Biomarker Assessments

Not applicable.

Safety Assessments

Safety will be assessed by monitoring and recording all adverse events (AEs). Additionally, safety assessments will consist of physical and neurological examinations, vital signs, 12-lead ECG, clinical laboratory test (hematology, blood chemistry, and urinalysis), and (for women of childbearing potential only) pregnancy test. A full neurological examination will be conducted during the Screening Visit. An abbreviated neurological examination will be performed on each treatment day (predose and at 4 hours postdose), and during Follow-up/Early Discontinuation visit.

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

Other Assessments

Not applicable.

Bioanalytical Methods

Plasma concentrations of E2082 will be measured using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method.

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

Secondary Endpoints

- Mean change from baseline in the PPR range in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- Onset, maximum change, and duration of response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- Frequency and percentage of subjects with complete suppression, partial response, and no response of SPR
- Changes from baseline in BL-VAS
- Incidence of treatment-emergent adverse events (TEAEs)
- Clinically significant changes from baseline in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2082, compared to placebo
- PK parameters of E2082 (C_{max}, time to reach C_{max} following drug administration [t_{max}], area under concentration-time curve from time 0 to 8 hours postdose [$AUC_{(0\text{-}8h)}$])

Exploratory Endpoints

- Relationship between plasma exposure of E2082 (PK) and PD response (eg, onset, maximum change, and duration of photosensitivity response, BL-VAS)

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 PK 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 PD 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, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

The Safety Analysis Set will be used for listings of individual E2082 plasma concentrations. The PK analysis set will be used for summaries of plasma E2082 concentrations and for analyses, 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 E2082. 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 E2082 will be analyzed based on available data from this study. The PK and PD Analysis Sets will be used to evaluate the relationship of PK of E2082 and change in SPR response. PK-PD analyses may include the examination of the relationship of PK of E2082 and SPR (eg, time of onset, maximum change, and duration of response; and BL-VAS data) using model-based approaches, data permitting. Details of the PK/PD analyses will be described in a separately prepared analysis plan and its report.

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 in the most sensitive and 3 eye conditions will be analyzed using a mixed effects model for the crossover part of the study and summarized for each E2082 dose level and placebo regardless of crossover design. The mixed effects model for the crossover part of the study will include treatment (E2082 2.5 mg, 25 mg, and placebo), 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 E2082 dose (2.5 mg or 25 mg) compared to placebo, and 90% CIs will be presented with no adjustments for multiplicity.

Additional analysis by graphical exploration for the evaluation of onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions for each treatment. Similarly, frequency and percentage of subjects with complete suppression, partial suppression, and no response at each dose level of E2082 will be summarized descriptively and graphically for each treatment.

Sensitivity analyses may be conducted for photosensitivity response, for example, in subjects who completed all 3 Treatment Periods 1 through 3 versus those who are included in the PD Analysis Set. Other exploratory analyses may be conducted as data permit.

All other PD data (ie, BL-VAS) 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.

Pharmacogenomic and Other Biomarker Analyses

Not applicable.

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. 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
AMPA	α amino 3 hydroxy-5-methyl-4-isoxazolepropionic acid
AST	aspartate aminotransferase
$AUC_{(0\text{-}8h)}$	area under concentration-time curve from time 0 to 8 hours postdose
β-hCG	beta-human chorionic gonadotropin
BL	Bond-Lader
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
CYP	cytochrome P450
EEG	electroencephalogram
GTCS	generalized tonic-clonic seizure
hCG	human chorionic gonadotropin
IB	Investigator's Brochure
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
LFT	liver function test
LNH	low/normal/high
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetics
POC	proof-of-concept

Abbreviation	Term
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_{max}	time at which the highest drug concentration occurs (time to reach C_{max} following drug administration)
ULN	upper limit of normal
WBC	white blood cell
VAS	Visual Analogue Scale
VNS	vagus nerve stimulation

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/she 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 study is defined as the last subject completing the Follow-up Visit. 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 CFR (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.

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 overall development plan of E2082 will be based on the potential role of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist as an antiepileptogenesis agent in a number of neurological disorders associated with glutamate-mediated neuronal overexcitation.

7.1.1 Mechanism of Action – E2082

E2082 is a selective noncompetitive AMPA type glutamate receptor antagonist. AMPA receptors, located on post-synaptic neurons, are responsible for fast glutamate-mediated excitation at synapses. Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS) and is implicated in a number of neurological disorders caused by neuronal overexcitation.

E2082 demonstrated potent in vitro inhibitory effect (AMPA receptor functional assay) and in vivo antiseizure effect in various animal models of epilepsy (audiogenic seizure, maximal electroshock [MES] seizure, and pharmacoresistant 6 Hz psychomotor seizure mouse models). Preclinical evidence suggests that E2082 showed a broad window between therapeutic effect and AMPA receptor antagonism-related CNS side effects (eg, sedation, ataxia) with a protective index (TD_{50} [rotarod test]/antiseizure ED_{50}) of 3.2- to 20-fold. Refer to the Investigator's Brochure (IB) for detailed information.

7.1.2 Clinical Experience With E2082

E2082 is currently under Phase 1 clinical development that comprises the first-in-human, double-blind, placebo-controlled, single- and multiple-ascending dose (SAD-MAD) study (E2082-J081-001; Study 001) in healthy male subjects in Japan. The SAD portion of Study 001 (Part A) evaluated pharmacokinetics (PK), safety and tolerability of E2082 in healthy male adult subjects at doses of 0.2, 0.5, 1, 2.5, 5, 10, 15, 25, and 40 mg under fasted condition, as well as at 5 mg under fed condition, and in elderly subjects at 10 mg. E2082 was administered as oral tablets (0.5 or 5-mg dose strengths) in all dose cohorts, except for the 0.2-mg cohort (as oral solution). The SAD portion of Study 001 is completed, in which a total of 60 subjects received a single dose of E2082 (0.2 through 40 mg) and 20 subjects received placebo. The MAD portion of Study 001 is ongoing.

7.1.2.1 Pharmacokinetics

Preliminary PK data suggest that E2082 was rapidly absorbed with median time to maximum plasma concentration (t_{max}) observed approximately 1 to 4 hours following oral administration of E2082 tablets over the dose range of 0.5 to 40 mg. The average half life of E2082 was approximately 30 hours. The mean plasma exposure (peak plasma concentration [C_{max}] and area under the plasma concentration-time curve from zero time extrapolated to infinite time [$AUC_{(0\text{-inf})}$]) increased approximately dose proportionally with increasing dose across the dose

range of 0.5 to 40 mg. Food intake did not appear to affect the rate or extent of E2082 absorption. Refer to the IB for a full description of PK.

7.1.2.2 Pharmacodynamics

Saccadic eye movements was included in Study 001 for evaluation of potential CNS-related side effects of E2082 as an exploratory pharmacodynamic (PD) parameter. Preliminary results suggest a dose/concentration-dependent reduction in peak saccadic velocity following single-dose administration of E2082. Refer to the IB for detailed information.

7.1.2.3 Safety and Tolerability

Preliminary safety data from Study 001 showed that E2082 was well-tolerated following single oral dose administration in healthy subjects. There were no deaths, serious adverse events (SAEs), or adverse events leading to discontinuation, and no medically significant findings from laboratory tests, ECG, or vital signs. A total of 16 subjects experienced treatment-emergent adverse events (TEAEs); 15/60 (25%) subjects receiving E2082 and 1/20 (5%) in the placebo group. The most common TEAEs reported were dizziness (14/60 [23.3%] subjects) and somnolence (6/60 [10.0%] subjects), followed by nausea (2/60 [3.3%] subjects), decreased appetite (2/60 [3.3%] subjects), back pain (1/60 [1.7%] subjects), and nasopharyngitis (1/20 [5.0%] subjects). All TEAEs were deemed related to E2082, except for back pain and nasopharyngitis. All TEAEs reported were mild to moderate in severity, and all resolved without any medical interventions.

Please refer to IB for a full summary of TEAEs, including safety and tolerability information.

7.2 Study Rationale

7.2.1 Photosensitivity Proof-of-Concept Model

Patients with epilepsy often have intermittent seizures that occur at variable times. Consequently, studies evaluating new antiseizure medications require that large numbers of subjects be evaluated over several months of treatment to accurately assess treatment effects. In such circumstances, it is extremely useful to conduct a “proof-of-concept” (POC) study, which would screen potential antiseizure agents for possible efficacy before proceeding to lengthy and expensive studies that expose many subjects to a new compound. The photosensitivity POC study design has been used successfully to evaluate potential antiseizure effects of new agents in early stage development in small groups of subjects with photically-induced generalized epileptiform responses on electroencephalogram (EEG), called photoparoxysmal responses (PPRs).

Photosensitivity describes the ability to produce epileptiform activities in response to intermittent photic stimulation. This EEG pattern is called PPR. Some subjects who are photosensitive have photosensitive epilepsy, and may have clinical events in response to photic stimulation. This response is also characterized as “reflex epilepsy” in the small group of subjects with epilepsy who have seizures in response to photic stimulation in the absence of adequate treatment. Many other subjects will have PPR demonstrated only as an EEG pattern. Photosensitivity is typically

a genetic trait with a Mendelian autosomal dominant pattern. When associated with epilepsy, the epilepsy type will almost always be classified as generalized idiopathic epilepsy, and the clinical seizure semiology will be characterized by absence, generalized tonic-clonic, or myoclonic seizures. Any of these 3 generalized seizure types can be precipitated by photic stimulation.

In the photosensitivity study design model, subjects who have PPR in response to flickering diffuse white light are included. A photosensitivity range for each subject can be determined by eliciting the upper and lower limits of sensitivity to intermittent photic stimulation (IPS) in order not to evoke seizures for that particular subject. Subjects are usually sensitive to IPS within clearly defined limits of flash frequency (mostly between 10-30 Hz). The photosensitivity range is relatively stable over time for each subject, although it can decrease or be eliminated by the use of antiepileptic drugs (AEDs).

This photosensitivity range, defined as the difference between the highest and lowest flash rates that consistently elicit a PPR, can be used as a quantitative measure of photosensitivity and, therefore, epileptogenicity. In photosensitivity studies, a stable baseline is defined as the baseline at the Screening and Predose on the day of each Treatment Period. Usually during a photosensitivity study, the baseline is stable throughout the study. The photosensitivity range is measured repeatedly (up to 8 times) over the course of a single day, and the range can be measured rapidly (over a 5-minute interval) in an EEG laboratory. Reduction in the photosensitivity range can then be easily quantified after a single dose of an AED. This reduction has been used to demonstrate an antiepileptic effect for a number of AEDs currently marketed or in development, most notably valproate, levetiracetam, lamotrigine, brivaracetam, carisbamate, JZP4 (Jazz Pharmaceuticals), cenobamate (YKP3089, SK Life Sciences), and selurampanel (BGG492, Novartis). This POC model has been successful in identifying multiple drugs in early phase drug development that were subsequently effective in large clinical studies (Binnie, et al., 1986a; Binnie, et al., 1986b; Binnie, 1988; Kasteleijn-Nolst Trenité, et al., 1996; Kasteleijn-Nolst Trenité, et al., 2007; Trenité, et al., 2007; French and Krauss, 2014; Kasteleijn-Nolst Trenité, et al., 2015).

The intent of this study is to provide a POC signal and evidence of a dose-response relationship, and to inform the design and dose selection for Phase 2 of the clinical development program.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to assess PD activity of E2082 as measured by suppression of epileptic PPR in the subject's most sensitive eye condition in the photosensitivity model as a proof of principle of efficacy in subjects with photosensitive epilepsy, compared to placebo.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the PD activity of E2082 as measured by suppression of PPR in each of the 3 eye conditions (eye closure, eyes closed, and eyes open), compared to placebo
- To assess PD activity of E2082 as measured by onset, maximum change, and duration of photosensitivity response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- To assess proportion of subjects with complete suppression, partial suppression, and no response of standardized photosensitivity response (SPR)
- To assess other CNS-related effects of E2082 based on Bond-Lader Visual Analogue Scale (BL-VAS)
- To assess the safety and tolerability of E2082 following single oral dose administration
- To assess the PK of E2082 following single oral dose administration

8.3 Exploratory Objective

- To explore relationships between PK and PD

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, double-blind, randomized, 6-sequence, 3-treatment, 3-period, crossover study with an Open-label Treatment Period, in adult subjects with photosensitive epilepsy. This study will use the photosensitivity proof of principle model to determine the potential of E2082 to reduce the photosensitive range in adult subjects.

This study will have 2 phases: Pretreatment Phase and Treatment Phase. The Pretreatment Phase will consist of a Screening Period (up to 3 weeks from Visit 1), during which each subject's study eligibility will be determined. The Treatment Phase will consist of 3 blinded Treatment Periods for a randomized crossover design, followed by an Open-label Treatment Period. During the Randomized Crossover Treatment Periods, there will be 3 Treatment Visits (Visit 2 [Treatment Period 1], Visit 3 [Treatment Period 2], and Visit 4 [Treatment Period 3]) evaluating single-dose administrations of either placebo, E2082 2.5 mg, or E2082 25 mg in a blinded manner.

Scenario 1: Newly enrolled or ongoing subjects who have completed upto the Treatment Period 3 at the time of Protocol Amendment 01 implementation, will undergo 1 treatment visit (Visit 5 [Treatment Period 4]) during the Open-label treatment period to receive a single-dose administration of E2082 40 mg or 10 mg; the dose to be administered will be provided by an independent unblinded biostatistician upon review of the subject's PPR data collected during Treatment Periods 1 through 3. (revised per Amendment 01)

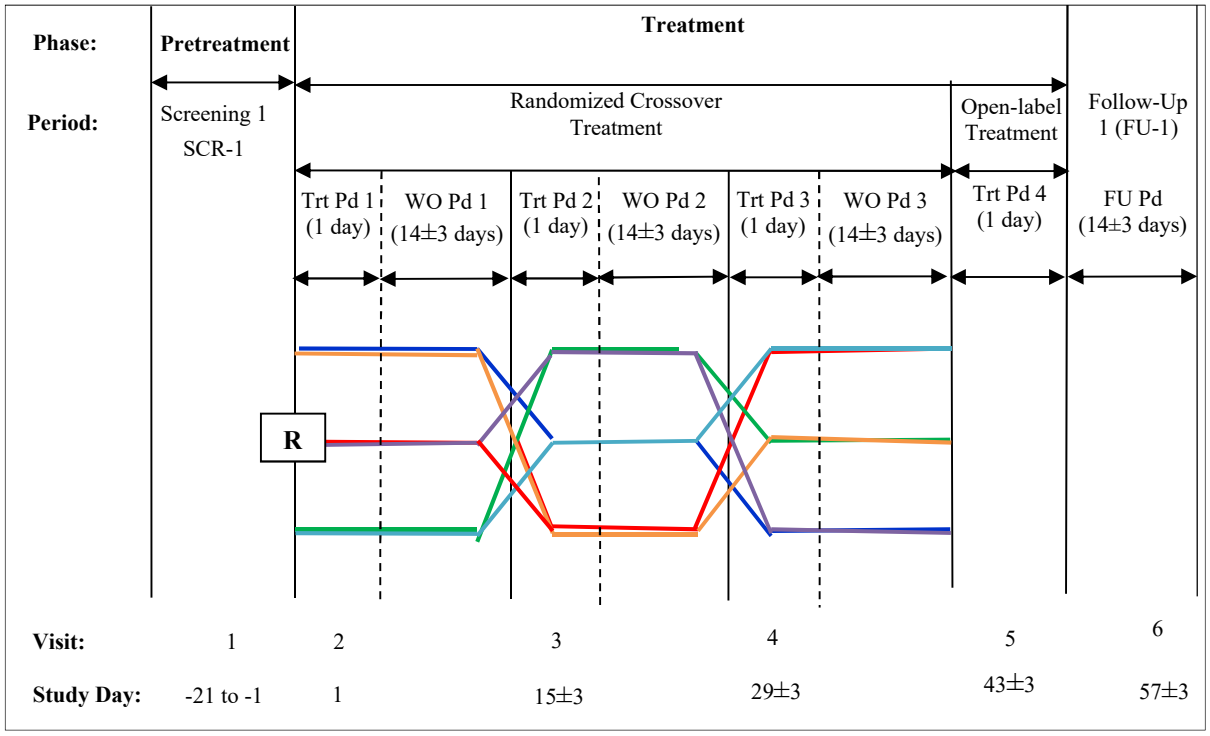
Scenario 2: Subjects who completed the open-label Treatment Period 4 (Visit 5), and have not completed the Follow-Up visit [Visit 6]) by the time of Protocol Amendment 01 implementation may continue in the study to receive an additional open-label, single oral dose of E2082 10 mg in the Treatment Period 5 (Visit 8) without undergoing Follow-up Visit 1 (Visit 6) and Screening 2 (Visit 7). (revised per Amendment 01)

Scenario 3: Subjects who completed the study (including Follow-Up visit [Visit 6]) before the implementation of Protocol Amendment 01 may be allowed to re-enter the study to receive an open-label, single-dose administration of E2082 10 mg after Screening 2 (Visit 7). (revised per Amendment 01)

Treatment visits (ie, Visit 2, Visit 3, Visit 4, and Visit 5) will each be separated by a 2-week (±3 days) washout interval for a total of approximately 6 weeks. Treatment Period 5 (Visit 8) will be 2 weeks (±3 days) after Treatment Period 4 (Visit 5) for subjects in Scenario 2, and after Screening 2 for subjects in Scenario 3. (revised per Amendment 01).

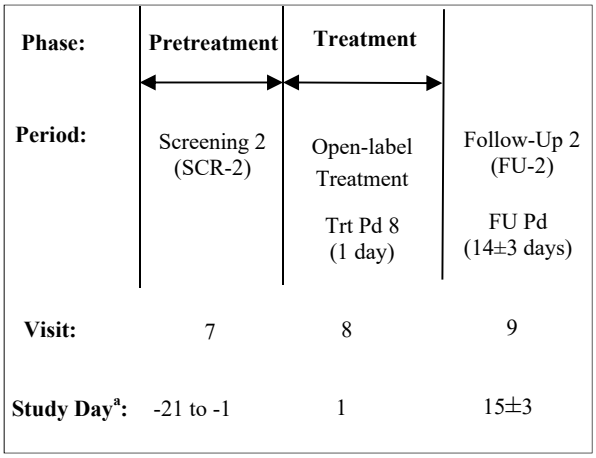
All subjects will undergo a Follow-up Period of 2 weeks (±3 days) after the last day of study product administration (Visit 5 and/or Visit 8, as applicable). (revised per Amendment 01). The anticipated study participation duration for each subject is approximately 11 to 15 weeks. All visits will be conducted on an outpatient basis.

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



Note: FU visit is a single visit at the end of the Follow-up Period.
FU = Follow-up, Pd = Period, R = Randomization, SCR = screening, Trt = Treatment, WO = Washout.

Figure 1 Study Design for Study E2082-A001-201- Scenario 1 (Revised per Amendment 01)



FU = Follow-up, SCR = screening, Pd = Period

a: Study days are with respective to the day of Treatment Period 5 (Visit 8). (revised per Amendment 01)

Figure 2 Study Design for Subjects in E2082-A001-201 - Scenario 3 (Revised per Amendment 01)

9.1.1 Pretreatment Phase

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks from Visit 1, and as applicable, Visit 7) (revised per Amendment 01), during which each subject's study eligibility will be determined.

9.1.1.1 Screening Period

Screening will occur between Day –21 and Day –1 of Visit 1, and, as applicable, Visit 7 (revised per Amendment 01). The purpose of the Screening Period is to establish protocol eligibility. Signed informed consent must be obtained before any study procedures (including screening procedures) can be conducted. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis and/or history of a PPR on EEG (ie, photosensitive epilepsy) for which they may receive up to 3 concomitant AEDs (Section 9.4.7).

At the Screening Visit (Visit 1 and, as applicable, Visit 7) (revised per Amendment 01), subjects will undergo an IPS-EEG assessment in 3 eye conditions (eye closure, eyes closed, and eyes open) at ascending and then descending photo-stimulation frequencies. At the Screening Visit, each frequency will be assessed in 3 eye conditions (eye closure, eyes closed, and eyes open) commencing at 2 Hz. As soon as generalized EEG epileptiform activity appears, the stimulation for that particular frequency in that particular eye condition will be instantly terminated. For the other eye conditions, ascending frequencies will be used, until generalized epileptiform activity is seen. This procedure will determine the lower threshold frequencies for each eye condition. Similar assessments will then be carried out starting at 60 Hz and descending through the standard frequencies. To avoid occurrence of a seizure, the stimulator will be turned off immediately if a generalized response is observed, and the sequence will be stopped at that point in that specific eye condition. In this manner, for each eye condition, the upper threshold frequencies are determined.

During the Screening Visit (Visit 1 and, as applicable, Visit 7) (revised per Amendment 01), IPS-EEG assessment will be performed at 5 time points, over a 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. However, the final determination of study eligibility will include predose assessments when the subject returns to study site for Visit 2 and as applicable, Visit 8. The Screening assessments will be conducted, including determination of the lower and upper limit of photosensitivity to IPS-EEG threshold frequency for each eye condition. Qualified medical personnel for the management of acute seizures will be present during the day of IPS-EEG procedure throughout the study.

Upon review by the investigator, subjects whose Screening assessments (including Day 1 [Visit 2] and [Visit 8] predose procedures [revised per Amendment 01]) continue to meet all of the inclusion/exclusion criteria will enter the Treatment Phase.

9.1.2 Treatment Phase

The duration of the Treatment Phase will be 6 weeks and will include 3 blinded Treatment Periods for a randomized crossover design, followed by an Open-label Treatment Period.

Up to 3 concomitant AEDs (Section 9.4.7) are allowed during the course of the study, provided that the dosage of concomitant AED(s) has remained stable for at least 4 weeks or 5 half-lives, whichever is longer, before Screening. In the case where a new AED regimen has been initiated for a subject, the subject must be on the new AED for at least 8 weeks and the dose must have remained stable for at least 4 weeks or 5 half-lives, whichever is longer, before screening. During the study, changes to concomitant AEDs (including dosage) are not permitted unless medically necessary and upon consultation with the Sponsor. Adherence to a stable AED regimen is critical as missed doses or changes during the study may affect the subject's photosensitivity response.

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.

9.1.2.1 Randomized Crossover Treatment Periods (Treatment Periods 1 to 3)

During the Randomized Crossover Treatment Periods, there will be 3 Treatment Visits (Visit 2 [Treatment Period 1], Visit 3 [Treatment Period 2], and Visit 4 [Treatment Period 3]) evaluating single-dose administrations of either placebo, E2082 2.5 mg, or E2082 25 mg. Subjects will be randomly assigned to 1 of 6 treatment sequences to receive the 3 treatments, in a blinded manner in a cross-over sequence according to his/her randomization code (Table 1).

Table 1 Treatment Sequences

Sequence	Treatment Period 1 (Visit 2)	Treatment Period 2 (Visit 3)	Treatment Period 3 (Visit 4)
1: ABC	Placebo	E2082 2.5 mg	E2082 25 mg
2: BCA	E2082 2.5 mg	E2082 25 mg	Placebo
3: CAB	E2082 25 mg	Placebo	E2082 2.5 mg
4: ACB	Placebo	E2082 25 mg	E2082 2.5 mg
5: BAC	E2082 2.5 mg	Placebo	E2082 25 mg
6: CBA	E2082 25 mg	E2082 2.5 mg	Placebo
A = Placebo; B = E2082 2.5 mg; C = E2082 25 mg			

On the day of each Treatment Visit (ie, Visit 2, Visit 3, and Visit 4), subjects will arrive at the clinic in the morning following an overnight fast of at least 8 hours. In order to enable discrimination between spontaneous and IPS evoked discharges, the subject will be assessed, at the start of each treatment day (ie, Visit 2, Visit 3, and Visit 4), for ≥2.5 minutes with each of the

3 eye conditions without any stimulation. Baseline IPS-EEG assessments will be conducted 30 minutes to 2 hours before study product administration on each treatment day, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency for each eye condition. The predose assessment serves as the baseline on each treatment day. Trains of flashes at constant frequency will be delivered for 4 to 6 seconds. Intervals between successive flash trains at a given frequency will last for at least 5 seconds. Determination of the photosensitivity ranges will be assessed with separate trains of flashes of 4 to 6 seconds duration (or less if generalized epileptic activity occurs). Flashes will be administered at standard frequencies of 2, 5, 8, 10, 13, 15, 18, 20, 23, 25, 30, 40, 50, and 60 Hz. IPS-EEG assessments will be repeated at 1, 2, 4, 6, and 8 hours (within ±15 minutes of each scheduled time point) following study product administration. PK, PD (B-L VAS), and vital signs assessments will be conducted predose, and at the same postdose time points as IPS-EEG measurements. Other safety assessments will be performed on each treatment visit day either predose only (clinical laboratory tests, Columbia-Suicide Severity Rating Scale (C-SSRS), and urine pregnancy test [for women of childbearing potential only]), or both predose and at 4 hours postdose (brief neurological and 12-lead ECG examinations).

9.1.2.2 Open-label Treatment Period

For subjects in Scenario 1, there will be 1 open-label treatment visit (Visit 5 [Treatment Period 4]) evaluating single oral dose administration of E2082 40 mg or 10 mg.

For subjects in Scenarios 2 and 3, there will be 2 open-label treatment visits: Treatment Period 4 to receive a single oral dose E2082 40 mg and Treatment Period 5 to receive E2082 10 mg. (revised per Amendment 01).

Subjects will return to the study site after the 2-week [±3 days] washout interval following the Randomized Crossover Treatment Period 3 and will receive a single dose of 40 mg or 10 mg E2082. The same study procedures for Treatment Periods 1 through 3 (ie, Visit 2, Visit 3, and Visit 4) will apply to Treatment Period 4 (ie, Visit 5) as well as Treatment Period 5 (Visit 8) (revised per Amendment 01), except that study drug administration is not blinded. Concomitant medication restrictions from the Randomized Crossover Treatment Period will apply to the Open-label Treatment Period.

9.1.3 Follow-Up Period

After completion of the Open-label Treatment period, subjects will enter the Follow-up Period, during which they will be required to complete a Follow-up visit (Visit 6) at 2 weeks ±3 days following the last day of study product administration.

For subjects in Scenario 2 and 3, the Follow-up (Visit 9) visit will be 2 weeks ±3 days after Treatment Period 5 (Visit 8). (revised per Amendment 01)

At the end of the Follow-up Period, subjects will be required to complete a Follow-up visit.

9.2 Discussion of Study Design, Including Choice of Control Groups

Randomization will be used in this study in the Randomized Crossover Treatment Periods 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 65 years of age at the time of informed consent.
2. A diagnosis and/or history of a PPR on EEG (ie, photosensitivity epilepsy).
3. If currently being treated with AED(s), up to a maximum of 3 concomitant AEDs is allowed provided that doses must have remained stable for at least 4 weeks or 5 half-lives, whichever longer, before Screening. In the case where a new AED regimen has been initiated for a subject, the subject must be on the new AED for at least 8 weeks before Screening and the dose must have remained stable for at least 4 weeks or 5 half-lives, whichever is longer, before Screening. (See Exclusion Criteria No. 17-22 for AEDs that are exclusionary). (revised per Amendment 01)
4. Reproducible IPS-induced PPR on EEG of at least 3 points on the SPR scale in at least 1 eye condition (eye closure, eyes closed, eyes open) on at least 3 of the EEGs performed at Screening.
5. Body mass index (BMI) between 18 to 35 kg/m^2 (inclusive) and a total body weight greater than or equal to 45 kg at Screening.
6. Agrees to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period before each treatment day.
7. Willing and able to comply with all aspects of the protocol.

Note: Subjects who have completed the study per original protocol may re-enter the study provided that the subject meet inclusion criteria No. 2 to 7. (revised per Amendment 01)

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 [β-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of β-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 before Screening.
6. Ongoing or history of generalized tonic-clonic seizures (GTCS) within 6 months before Screening.
7. Subject who had developed a clinical seizure during previous PPR assessment, or who experiences a clinical seizure during the Screening IPS procedure.
8. Frequent spontaneous background burst or current evidence of proconvulsive activity on EEG (eg, increase in spike-wave activity) at Screening.
9. Inability to follow restriction on watching television, or use of any device(s) with an animated screen (eg, computer, video games, tablets, or smart phone) from the time of arrival at the study center until study procedures are completed for that day.

10. Currently active 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. 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 using Fridericia formula (QTcF) interval; or prolonged QT/QTcF interval (QTcF >450 msec) demonstrated on ECG at Screening or Baseline (based on average of triplicate ECGs).
12. Presence of 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.
13. Current/ongoing clinically significant active liver disease, porphyria, or with a family history of severe hepatic dysfunction indicated by abnormal liver function tests (LFTs) greater than 3 times the upper limit of normal (ULN) (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).
14. Any history of gastrointestinal conditions or surgery that may affect PK profiles of E2082 (eg, hepatectomy, nephrectomy, and digestive organ resection).
15. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening.
16. Use of perampanel within 6 weeks before Screening.
17. Use of felbamate for less than 2 years or where the dose has not been stable for at least 8 weeks before Visit 1. Subject must not have a history of white blood cell (WBC) count below equal or less than 2500/μL (2.50 1E+09/L), platelet count below 100,000, LFTs above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If subjects received felbamate in the past, it must have been discontinued 8 weeks before Visit 1 to be eligible for study participation.
18. Use of vigabatrin within 5 months before Screening. Subjects who have discontinued vigabatrin for at least 5 months before Screening must have documentation showing no evidence of vigabatrin associated clinically significant abnormality in a visual perimetry test in order to be eligible for the study.
19. Concomitant use of cannabinoids.
20. Use of benzodiazepines for epilepsy for which the dose has not been stable for greater than 4 weeks before Screening. Benzodiazepine use as rescue medication for seizure control is allowed; however, intermittent use of benzodiazepines for any other indication (eg, anxiety/sleep disorders) is prohibited.
21. Use of concomitant AEDs or other drugs that are known to be potent cytochrome P450 (CYP)3A enzyme inducers (such as carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, phenobarbital, and primidone) or CYP3A inhibitors within 4 weeks or 5 half-lives, whichever is longer, before screening. In addition, consumption of dietary supplements, foods, and forms of fruit juice that may affect the expression or function of CYP3A within 14 days before study drug administration. (revised per Amendment 01)
22. Vagus nerve stimulation (VNS) implanted within 5 months or changes in parameter within 4 weeks before Screening.

23. On a ketogenic diet for which the diet is not a stable regimen for at least 4 weeks before Screening.
24. History of drug or alcohol dependency or abuse within the 12 months before Screening, or those subjects who have a positive drug test or alcohol test at Screening.
25. History of or ongoing multiple drug allergies or severe drug reaction to AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
26. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
27. 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).
28. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS).
29. 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.
30. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5 half-lives, whichever is longer, preceding informed consent, except the investigational study for the evaluation of commercial IPS machine.

    Note: Subjects in Scenario 3 will not be allowed to re-enter the study if they meet any of the exclusion criteria listed above

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.

Subjects who discontinue from the study early may be replaced upon consultation with the sponsor.

9.3.3.1 IPS-EEG-Specific Subject Withdrawal/Stopping 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.

At the discretion of the investigator, a subject may be withheld from further IPS-EEG testing during a study visit or withdrawn from the study if any of the following 3 circumstances occur:

1. If a subject experiences:

   a) GTCS on any study day, and the subject has not had a GTCS in the 6 months before enrollment, that subject will be discontinued from the study.

   OR

   b) GTCS during photic stimulation, 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, that

subject will be discontinued from the study.
Proconvulsive activity is defined as

a) 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; or

b) change in the usual pattern of PPR that is typical for the subject such as: decrease in time to occurrence of PPRs at the same flash frequency; increase in the duration of the PPR; or, clear increase of PPR-related negative sensations (clinical signs) or appearance or increase of spontaneous epileptiform activity.

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

9.4 Treatments

9.4.1 Treatments Administered

9.4.1.1 Randomized Crossover Treatment Periods

The following treatments will be administered as a single oral dose (Table 2). Each subject will receive each treatment in a sequence according to the randomization code (Table 1).

Table 2 Treatment Description

Treatment	Study Drug/Dose	Study Drug(s) to be Administered
A	Placebo	5 x E2082-matched placebo tablets
B	E2082 2.5 mg	5 x E2082 0.5-mg tablets
C	E2082 25 mg	5 x E2082 5-mg tablets

9.4.1.2 Open-label Treatment Period

Each subject will receive a single oral dose of E2082 40 mg (8 x E2082 5-mg tablets) and/or 10 mg (2 x E2082 5-mg tablets). Dose selection (10 or 40 mg) will depend on the individual subject's PPR during the blinded Treatment Periods as described in Section 9.1. (revised per Amendment 01)

9.4.2 Identity of Investigational Products

E2082 film-coated tablets (0.5 mg and 5 mg) and corresponding placebo are yellowish red, approximately 5.1 mm in diameter. Test drug and placebo will be supplied by the sponsor in labeled containers.

9.4.2.1 Chemical Name, Structural Formula of E2082

- Test drug code: E2082

- Generic name: Not Applicable
- Chemical name: 2-Fluoro-6-[3-fluoro-8-oxo-7-(pyridin-3-yl)-7,8-dihydro-6*H*-pyrano[3,2-*b*:5,4-*b'*]dipyridin-9-yl]benzonitrile
- Molecular formula: $C_{23}H_{12}F_2N_4O_2$
- Molecular weight: 414.37

9.4.2.2 Comparator Drug

Placebo tablet with matching color and appearance to E2082 tablet will be supplied.

9.4.2.3 Labeling for Study Drug

E2082 will be labeled in accordance with text that is in full regulatory compliance.

9.4.2.4 Storage Conditions

E2082 will be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that E2082 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

9.4.3.1 Randomized Crossover Treatment Periods

Subjects will be assigned to all 3 treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent, unblinded, statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

9.4.3.2 Open-Label Treatment Period

Each subject will receive a single oral dose of E2082 40 mg (8 x E2082 5-mg tablets) and/or 10 mg (2 x E2082 5-mg tablets), as applicable based on blinded review of the subject's PPR during Treatment Periods 1 through 3 as described in Section 9.1. (revised per Amendment 01)

9.4.4 Selection of Doses in the Study

Single oral doses of 2.5 mg to 40 mg are selected for detection of pharmacodynamics response in patients with photosensitivity epilepsy in this study. (revised per Amendment 01)

The low dose of 2.5 mg was selected based on the exposures observed at ED_{50} in preclinical mouse model (6 Hz psychomotor seizure model). Based on preliminary SAD PK data from Study 001, a single dose of 2.5 mg is expected to achieve plasma concentrations at or above the

predicted minimum effective plasma concentration of 80 ng/mL for approximately 8 hours in the majority of the subjects (Figure 3). The highest dose of E2082 tested in the first-in-human study (Study 001) was 40 mg and was found to be well tolerated (revised per Amendment 01). The proposed dose range between 2.5 mg and the highest dose of 40 mg are expected to provide a wide range of exposure (approximately 10- to 16-fold) to demonstrate POC and may also support exploratory PK/PD response analysis.

In addition to 2.5, 25 and 40 mg, 10 mg is being added in Protocol Amendment 01 in order to better characterize dose/exposure-response relationship and to support dose recommendation for Phase 2/3 clinical studies in target patient population. (revised per Amendment 01)

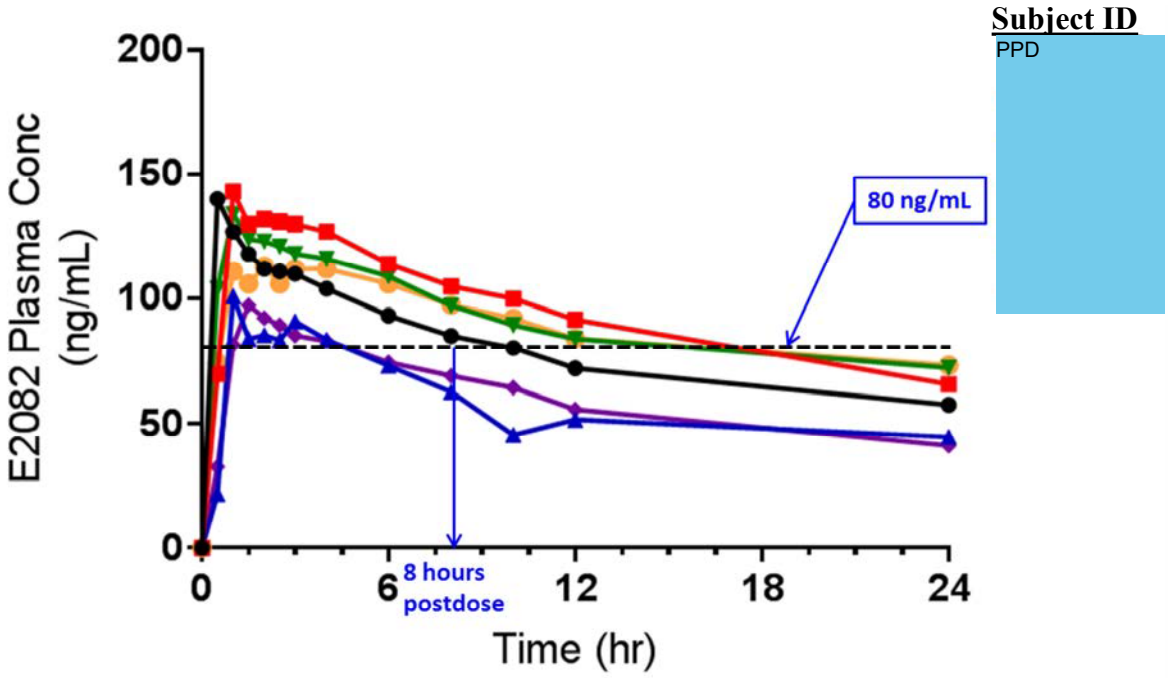


Figure 3 Individual plasma concentration-time profiles of E2082 (2.5 mg) following single oral dose administration in Study E2082-A001-001

conc = concentration

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, Visit 2, Visit 3, Visit 4, Visit 5, and, as applicable, Visit 8) (revised per Amendment 01). A light snack can be provided at 30 minutes predose (after clinical laboratory blood collection) and at 2 hours postdose.

9.4.6 Blinding

Central EEG reading of all EEG records (including Screening and Treatment Periods 1 through 4 and, Treatment Period 5, as applicable) (revised per Amendment 01) will be performed in a blinded and independent manner. Investigator(s) may consult with the central read only during the Pretreatment Phase, if needed, for IPS-EEG eligibility determination.

During the Randomized Crossover Treatment Periods, 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/designee (with the exception of the independent biostatistician and unblinded CRAs) 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 E2082 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 tablets 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 (see also Section 9.5.4.5). 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 within 3 months before the Screening Visit and throughout the course of 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 a maximum of 3 concomitant AEDs (with the exception of those AEDs listed in Section 9.4.7.1) are allowed during the course of the study, provided that the dosage of concomitant AED(s) has remained stable for at least 4 weeks or 5 half-lives, whichever longer, before Screening. In the case where a new AED regimen has been initiated for a subject, the subject must be on the new AED for at least 8 weeks and the dose must have remained stable for at least 4 weeks or 5 half-lives, whichever is longer, before screening. During the study, changes to concomitant AEDs (including dosage) are not permitted unless medically necessary and upon consultation with the Sponsor.

Vagus nerve stimulation (VNS) is not considered as one of the 3 allowed concomitant AEDs. However, VNS implantation during the course of the study is prohibited. For subjects who have VNS implanted prior to participation in this study, changes to VNS parameters are not allowed unless medically necessary.

Likewise, ketogenic diet is not considered as one of the 3 allowed concomitant AEDs. However, changes to ketogenic diet (eg, median chain triglyceride level) are not allowed during the study.

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

Use of the following AEDs during the course of the study is not allowed:

- Perampanel
- Vigabatrin
- Cannabinoids
- Benzodiazepines for non-epilepsy indications (eg, anxiety/sleep disorders) (Stable doses of benzodiazepine or intermittent benzodiazepine use as rescue medication for seizure control is allowed)
- Enzyme-inducing antiepileptic drugs (EIAEDs, eg, carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, phenobarbital, and primidone)

Concomitant use of medications known to be potent CYP3A inducers/inhibitors including, but not limited to, rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, modafinil, pioglitazone, and rifabutin will not be permitted and are to be discontinued within 4 weeks or 5 half-lives, whichever longer before Visit 1, and, as applicable Visit 7.

9.4.7.2 Restrictions During the Study Period

Study drug will be administered on the day of each Treatment Visit (ie, Visit 2, Visit 3, Visit 4, Visit 5, and, as applicable, Visit 8) (revised per Amendment 01) after an overnight fast of at least 8 hours. Treatments will be administered orally 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 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.

For study visits where IPS-EEG assessments will be performed, subjects will be required to abstain from watching television or using any device with an animated screen (ie, computer, video games, tablets, or smart phone) from the time of arrival at the study center until study procedures are completed for that day. 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 before each treatment day. Subjects will be instructed to get similar amounts of sleep prior to each visit.

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/designee 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, and race/ethnicity.

9.5.1.2 Screening 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 the Screening Visit (Visit 1 and, as applicable Visit 7) (revised per Amendment 01), as specified in the Schedule of Procedures/Assessments (Table 4 ` Table 5). This sample will be tested for common drugs of use/abuse: eg, ethyl alcohol, phencyclidine (PCP), benzodiazepines, cocaine, amphetamines, cannabinoids, opioids, barbiturates, and tricyclic antidepressant drugs.

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, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples for the determination of plasma concentrations of E2082 will be collected from each subject. PK sampling for plasma concentration will be collected predose (within 2 hours) and postdose at 1 (±10 min), 2 (±10 min), 4 (±15 min), 6 (±15 min), and 8 (±15 min) hours on each treatment day (ie, Visit 2, Visit 3, Visit 4, Visit 5, and, as applicable, Visit 8) (revised per Amendment 01). Plasma concentrations of E2082 will be measured using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method. Actual PK sampling date and time will be recorded at each scheduled and unscheduled sampling time point. Actual date and time of study drug administration will also be recorded for each dose administration during each Treatment Visit. See Table 6 for a description of assessment timings and window periods.

At time points when vital signs, ECGs, and blood sampling are to be performed at the same time point, these procedures will be performed in the following order: ECGs, vital signs, and then blood sampling.

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, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

All PD assessments will be performed within ±15 minutes of the scheduled time point. See Table 6 for a description of assessment timings and window periods.

IPS-EEG

Throughout the study, the flash frequency will be recorded. Three eye conditions (eye closure, eyes closed, and eyes open) per stimulus for assessment purposes will be recorded. The combination of lower and upper frequencies gives a total of 3 photosensitivity ranges, 1 per eye condition. If there is any doubt of the interpretation during any of the assessments (for example blinking during the eyes open condition, provoking epileptiform activity) the stimulation in the same eye condition will be repeated. In order to minimize the risk of inducing a seizure, photic stimulation will not be carried out between the upper and lower thresholds. This method has been found to be the safest, as it prevents elicitation of seizures by avoiding stimulation of the subject at the most sensitive frequencies. The range for each subject will be recorded in the CRF. The most sensitive eye condition will be noted during every visit; however, assessments in all 3 eye conditions will be noted.

During the Screening Visit (Visit 1 and, as applicable, Visit 7) (revised per Amendment 01), IPS-EEG assessment will be performed at 5 time points, over a 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. However, the final determination of study eligibility will include predose assessments when the subject returns to study site for Visit 2.

PD activity of E2082 will be assessed by suppression of PPR following IPS under 3 eye conditions (eye closure, eyes closed, and eyes open) using the Grass PS 33 photic stimulator with an unpatterned glass lamp and an intensity of 100 cd/m^2/flash at approximately 30 minutes to 2 hours predose, and at 1, 2, 4, 6, and 8 hours postdose (within ±15 minutes of each scheduled time point), on each treatment day, (ie, Visit 2, Visit 3, Visit 4, Visit 5, and Visit 8) (revised per Amendment 01). The time course (30 minutes to 2 hours predose to 8 hours postdose) will help assess the onset, maximum change from baseline, and duration of the reduction in PPR response. The predose assessment serves as the baseline on each treatment day. PPR is expected to be within the range of 2 Hz to 60 Hz, depending on the subject's 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 epileptiform activity). 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

In order to enable discrimination between spontaneous and IPS evoked discharges, the subject will be assessed ,at the start of each treatment day, (ie, Visit 2, Visit 3, Visit 4, Visit 5, and, as applicable, Visit 8) (revised per Amendment 01), for ≥2.5 minutes with each of the 3 eye conditions without any stimulation. Each IPS-EEG assessment will be conducted in all 3 eye conditions (eye closure, eyes closed, and eyes open; each for a minimum of 2.5 minutes) at ascending and then descending photo stimulation frequencies. The lower and upper limit of photosensitivity to IPS threshold frequency will be determined for each eye condition. Trains of flashes at constant frequency will be delivered for 4 to 6 seconds. Intervals between successive flash trains at a given frequency will last for at least 5 seconds. Determination of the photosensitivity ranges will be assessed with separate trains of flashes of 4 to 6 seconds duration (or less if generalized epileptic activity occurs). Flashes will be administered at standard frequencies of 2, 5, 8, 10, 13, 15, 18, 20, 23, 25, 30, 40, 50, and 60 Hz.

Bond and Lader Visual Analogue Scale

The Bond and Lader VAS (Bond A, 1974) for CNS–related effects of E2082 (such as somnolence, sedation, dizziness, and body sway) will be evaluated for each subject predose (within 2 hours) and at 1, 2, 4, 6, and 8 hours postdose on each treatment day (ie, Visit 2, Visit 3, Visit 4, Visit 5, and, as applicable, Visit 8). (revised per Amendment 01)

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; pregnancy test for women of childbearing potential only; and the performance of neurological and physical examinations as detailed in Table 4 and Table 5.

An assessment of suicidality using the C-SSRS will be performed as detailed in Table 4 and 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 E2082.

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 (ie, Follow-up/Early Discontinuation Visit). SAEs must be collected for 28 days after the last dose.

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 QT interval corrected by the Fridericia formula (QTcF) 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, blood chemistry, and urinalysis, are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 4 and 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. Subjects will fast for at least 8 hours before blood is drawn for clinical laboratory assessments. Clinical laboratory blood collection must be performed before a subject can receive the light snack that can be provided at 30 minutes predose. See Table 6 for a description of assessment timings and window periods.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Blood 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], heart rate [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 4 and Table 5). Vital signs are to be taken in the supine position after subjects have remained resting for at least 5 minutes. All BP measurements should be performed on the same arm, preferably by the same qualified healthcare professional.

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 minimize the potential effects of blood drawing on recordings obtained during safety assessments.

At time points when vital signs, ECGs, and blood sampling are to be performed at the same time point, these procedures will be performed in the following order: ECGs, vital signs, and then blood sampling. Subjects will remain rested in the supine position for 10 minutes before and 5 minutes after ECG recordings, followed by recording of vital sign measurements.

See Table 6 for a description of assessment timings and window periods.

9.5.1.5.5 PHYSICAL EXAMINATIONS

Full and abbreviated physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 4 and 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. Clinically significant abnormal findings from the physical examination will be recorded as an AE on the AE CRF.

Full Physical Examination

A full 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

Full and abbreviated neurological examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 4 and 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. Clinically significant abnormal findings from the neurological examination will be recorded as an AE on the AE CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

ECGs (12-lead) will be obtained as designated in the Schedule of Procedures/Assessments (Table 4 and Table 5). At time points when vital signs, ECGs, and blood sampling are to be performed at the same time point, these procedures will be performed in the following order: ECGs, vital signs, and then blood sampling. Subjects will remain rested in the supine position for 10 minutes before and 5 minutes after ECG recordings, followed by recording of vital sign measurements.

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.

See Table 6 for a description of assessment timings and window periods.

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

C-SSRS

An assessment of suicidality using the C-SSRS will be performed at Screening, during each Treatment visit (ie, Visit 2, Visit 3, Visit 4, Visit 5, and, as applicable, Visit 8) (revised per Amendment 01), and at the Follow-up/Early discontinuation visit, as designated in the Schedule of Procedures/Assessments (Table 4 and Table 5). It is recommended that, for the Treatment Visits, C-SSRS be performed predose to ensure there is no increased risk of suicidality since last visit.

Pregnancy Test

For women of childbearing potential, a serum β-hCG or hCG test (6 mL blood sample) will be performed during Screening Visit (Table 4 and Table 5). Subsequently, urine pregnancy test will be performed prior to dose administration on each treatment visit (ie, Visit 2, Visit 3, Visit 4, and Visit 5, and, as applicable, Visit 8) (revised per Amendment 01), and upon return to site during Follow-up/Early Discontinuation Visit. Unscheduled pregnancy test (serum or urine) may be performed as medically necessary at the discretion of the investigator.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of procedures/assessments for the study.

Table 4 Schedule of Procedures and Assessments in E2082-A001-201

Phase	Pretreatment	Treatment				Follow-up[a] (FU-1)/Early Discontinuation[b]	Unscheduled Visit
		Randomized Crossover			Open-label		
Period	Screening 1 (SCR-1)	Trt Pd 1	Trt Pd 2	Trt Pd 3	Trt Pd 4		
Visit	**1**	**2**	**3**	**4**	**5**	**6[a]**	
Study Day	**-21 to -1**	**1**	**15±3**	**29±3**	**43±3**	**57±3[a]**	
Procedures/Assessments							
Informed Consent	X						
Demography	X						
Randomization		X					
Inclusion/exclusion criteria	X	X					
Medical and surgical history	X						
Epilepsy medical history	X						
Height[c] and weight	X	X				X	(X)[d]
Physical examination[e]	X	X				X	(X)[d]
Neurological examination[f]	X	X	X	X	X	X	(X)[d]
Vital signs[g,h]	X	X	X	X	X	X	(X)[d]
12-Lead ECG[i,h]	X	X	X	X	X	X	(X)[d]
Clinical laboratory tests[j,h]	X	X	X	X	X	X	(X)[d]
Serology (HBsAg, HCV Ab)	X						

Table 4 Schedule of Procedures and Assessments in E2082-A001-201

Phase	Pretreatment	Treatment				Follow-up[a] (FU-1)/Early Discontinuation[b]	Unscheduled Visit
		Randomized Crossover			Open-label		
Period	Screening 1 (SCR-1)	Trt Pd 1	Trt Pd 2	Trt Pd 3	Trt Pd 4		
Visit	**1**	**2**	**3**	**4**	**5**	**6[a]**	
Study Day	**-21 to -1**	**1**	**15±3**	**29±3**	**43±3**	**57±3[a]**	
Procedures/Assessments							
Urine drug test[k]	X						
Serum β-hCG [or hCG] test[l]	X						
Urine pregnancy test[l]		X	X	X	X	X	(X)[d]
PK sampling (plasma)[m,h]		X	X	X	X		(X)[d]
IPS-EEG Assessment	X[n]	X[o]	X[o]	X[o]	X[o]		
BL-VAS[p]		X	X	X	X		
C-SSRS[q]	X	X	X	X	X	X	(X)[d]
Study drug administration		X	X	X	X		
Prior and concomitant medication(s)	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

β-hCG = beta-human chorionic gonadotropin (or hCG = human chorionic gonadotropin), BL-VAS = Bond and Lader Visual Analogue Scale, C-SSRS = Columbia-Suicide Severity Rating Scale, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, IPS-EEG = intermittent photic stimulation electroencephalogram, Pd = Period, PK = pharmacokinetics, QTcF = QT interval corrected by the Fridericia formula, Trt = Treatment, VAS = visual analogue scale.

b: For subjects who completed Open-label Treatment Period. Follow-up visit is to be conducted 2 weeks ±3 days following the last day of study product administration.

Table 4 Schedule of Procedures and Assessments in E2082-A001-201

Phase	Pretreatment	Treatment				Follow-up[a] (FU-1)/Early Discontinuation[b]	Unscheduled Visit
		Randomized Crossover			Open-label		
Period	Screening 1 (SCR-1)	Trt Pd 1	Trt Pd 2	Trt Pd 3	Trt Pd 4		
Visit	1	2	3	4	5	6[a]	
Study Day	-21 to -1	1	15±3	29±3	43±3	57±3[a]	
Procedures/Assessments							

c: For subjects who discontinued early from the study after having been exposed to study drug, Early Discontinuation Visit is to be conducted 2 weeks ±3 days following the last dose administration. Early Discontinuation visit is not required for subjects who discontinued from the study before receiving the first study drug administration.

d: Height will be assessed only during the Screening Visit.

e: During the unscheduled visits, specific procedure(s) to be performed will be on an as-needed basis at the discretion of the investigator. For example, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.

f: A full physical examination will be conducted at Screening. Abbreviated physical examination will be performed during Visit 2 (before randomization) and Follow-up/Early Discontinuation Visit. Additional physical examination may be conducted at any other visit(s), as medically deemed necessary. Clinically significant abnormal findings from the physical examinations will be reported as AEs.

g: A full neurological examination will be conducted at Screening. Abbreviated neurological examination will be performed during each treatment visit (predose and at 4 hours [±30 min] postdose) and Follow-up/Early Discontinuation Visit. Clinically significant abnormal findings from the neurological examinations will be reported as AEs.

h: Vital signs (systolic and diastolic blood pressure [BP], heart rate [HR], respiratory rate, and body temperature) will be taken at Screening, during each treatment visit, and during Follow-up/Early Discontinuation Visit. On each treatment day (ie, Visit 2, Visit 3, Visit 4, and Visit 5), vital sign measurements will be obtained predose (within 2 hours), and at 1, 2, 4, 6, and 8 hours postdose, with the window for collection postdose is (±15 min) at each scheduled timepoint. Vital signs are to be taken in the supine position after subjects have remained resting for at least 5 minutes.

i: At time points when vital signs, ECG, and blood sampling are to be performed at the same time point, the following order must be followed: ECG, vital signs, and then blood sampling.

j: ECG assessments will be performed at Screening, during each treatment visit (predose and at 4 hours [±30 min] postdose), and during Follow-up/Early Discontinuation Visit. ECG measurements are to be taken in the supine position after subjects have remained resting for at least 5 minutes. If QTcF exceeds 450 msec during any visit, 3 consecutive ECG measurements each separated by 5 – 10 minutes will be performed to confirm the abnormality. Any ECG abnormalities that the investigator deems to be clinically significant will be reported

Table 4 Schedule of Procedures and Assessments in E2082-A001-201

Phase	Pretreatment	Treatment				Follow-up[a] (FU-1)/Early Discontinuation[b]	Unscheduled Visit
		Randomized Crossover			Open-label		
Period	Screening 1 (SCR-1)	Trt Pd 1	Trt Pd 2	Trt Pd 3	Trt Pd 4		
Visit	1	2	3	4	5	6[a]	
Study Day	-21 to -1	1	15±3	29±3	43±3	57±3[a]	
Procedures/Assessments							

as AEs.

k: Clinical laboratory tests include: hematology, blood chemistry, and urinalysis. Subjects will fast for at least 8 hours before blood is drawn for clinical laboratory assessments. Clinical laboratory blood collection must be performed before a subject can receive the light snack that can be provided at 30 minutes predose.

l: Screening for common drugs of use/abuse (eg, ethyl alcohol, phencyclidine (PCP), benzodiazepines, cocaine, amphetamines, cannabinoids, opioids, barbiturates, and tricyclic antidepressant drug).

m: For female subjects of childbearing potential only.

n: Blood samples for plasma PK will be obtained predose (within 2 hours) and at 1 (±10 min), 2 (±10 min), 4 (±15 min), 6 (±15 min), and 8 (±15 min) hours postdose on each treatment day (ie, Visit 2, Visit 3, Visit 4, and Visit 5).

o: During Screening Visit, IPS-EEG assessment will be performed at 5 time points over a 4-hour interval (0, 1, 2, 3, and 4 hours; within ±15 minutes of the scheduled time point).

p: On each treatment day (Visit 2, Visit 3, Visit 4, and Visit 5), IPS-EEG assessment will be performed predose (approximately within 30 minutes to 2 hours), and at 1, 2, 4, 6, and 8 hours postdose (a window of ±15 minutes is allowed at each postdose timepoint).

q: BL-VAS will be performed from each subject on each treatment day predose (within 2 hours) and at 1, 2, 4, 6, and 8 hours postdose.

r: C-SSRS will be performed at Screening, during each Treatment Visit (recommended to administer C-SSRS predose to ensure there is no increased risk of suicidality since last visit), and at the Follow-up/Early Discontinuation Visit.

Table 5 Schedule of Procedures and Assessments in E2082-A001-201 for Subjects in Scenario - 3 (Revised per Amendment 01)

Phase	Pretreatment	Open-Label Treatment	Follow-up[a] (FU-2) /Early Discontinuation[b]	Unscheduled Visit
Period	Screening (SCR-2)	Trt Pd 5		
Visit	**7**	**8**	**9**	
Study Day	**-21 to -1**	**1**	**14±3**	
Procedures/Assessments				
Informed Consent	X			
Demography	X			
Inclusion/exclusion criteria	X			
Medical and surgical history (any update)	X			
Epilepsy medical history (any update)	X			
weight	X		X	(X)[c]
Physical examination[d]	X		X	(X)[c]
Neurological examination[e]	X	X	X	(X)[c]
Vital signs[f,g]	X	X	X	(X)[c]
12-Lead ECG[h,g]	X	X	X	(X)[c]
Clinical laboratory tests[i,g]	X	X	X	(X)[c]
Serology (HBsAg, HCV Ab)	X			
Urine drug test[j]	X			
Serum β-hCG [or hCG] test[k]	X			
Urine pregnancy test[k]		X	X	(X)[c]
PK sampling (plasma)[l,g]		X		(X)[c]
IPS-EEG Assessment	X[m]	X[n]		
BL-VAS[o]		X		
C-SSRS[p]	X	X	X	(X)[c]
Study drug administration		X		
Prior and concomitant medication(s)	X	X	X	X
Adverse events	X	X	X	X

Note: Number of days added here with respective to the Treatment Period 5 (Visit 8)

β-hCG = beta-human chorionic gonadotropin (or hCG = human chorionic gonadotropin), BL-VAS = Bond and Lader Visual Analogue Scale, C-SSRS = Columbia-Suicide Severity Rating Scale, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, IPS-EEG = intermittent photic stimulation electroencephalogram, Pd = Period, PK = pharmacokinetics, QTcF = QT interval corrected by the Fridericia formula, Trt = Treatment.

a: For subjects who completed Open-label Treatment Period 5, Follow-up visit is to be conducted 2 weeks ±3 days following the last day of study product administration.

b: For subjects who discontinued early from the study after having been exposed to study drug, Early Discontinuation Visit is to be conducted 2 weeks ±3 days following the last dose administration. Early Discontinuation visit is not required for subjects who discontinued from the study before receiving the first study drug administration.

c: During the unscheduled visits, specific procedure(s) to be performed will be on an as-needed basis at the discretion of the investigator. For example, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.

d: A full physical examination will be conducted at Screening. Abbreviated physical examination will be performed during Visit 8 (before randomization) and Follow-up/Early Discontinuation Visit. Additional physical examination may be conducted at any other visit(s), as medically deemed necessary. Clinically significant abnormal findings from the physical examinations will be reported as AEs.

e: A full neurological examination will be conducted at Screening. Abbreviated neurological examination will be performed during the treatment visit (predose and at 4 hours [±30 min] postdose) and Follow-up/Early Discontinuation Visit. Clinically significant abnormal findings from the neurological examinations will be reported as AEs.

f: Vital signs (systolic and diastolic blood pressure [BP], heart rate [HR], respiratory rate, and body temperature) will be taken at Screening, during treatment visit, and during Follow-up/Early Discontinuation Visit. On treatment day (Visit 8), vital sign measurements will be obtained predose (within 2 hours), and at 1, 2, 4, 6, and 8 hours postdose, with the window for collection postdose is (±15 min) at each scheduled timepoint. Vital signs are to be taken in the supine position after subjects have remained resting for at least 5 minutes.

g: At time points when vital signs, ECG, and blood sampling are to be performed at the same time point, the following order must be followed: ECG, vital signs, and then blood sampling.

h: ECG assessments will be performed at Screening, during each treatment visit (predose and at 4 hours [±30 min] postdose), and during Follow-up/Early Discontinuation Visit. ECG measurements are to be taken in the supine position after subjects have remained resting for at least 5 minutes. If QTcF exceeds 450 msec during any visit, 3 consecutive ECG measurements each separated by 5 – 10 minutes will be performed to confirm the abnormality. Any ECG abnormalities that the investigator deems to be clinically significant will be reported as AEs.

i: Clinical laboratory tests include: hematology, blood chemistry, and urinalysis. Subjects will fast for at least 8 hours before blood is drawn for clinical laboratory assessments. Clinical laboratory blood collection must be performed before a subject can receive the light snack that can be provided at 30 minutes predose.

j: Screening for common drugs of use/abuse (eg, ethyl alcohol, phencyclidine (PCP), benzodiazepines, cocaine, amphetamines, cannabinoids, opioids, barbiturates, and tricyclic antidepressant drug).

k: For female subjects of childbearing potential only.

l: Blood samples for plasma PK will be obtained predose (within 2 hours) and at 1 (±10 min), 2 (±10 min), 4 (±15 min), 6 (±15 min), and 8 (±15 min) hours postdose on treatment day (Visit 8).

m: During Screening Visit, IPS-EEG assessment will be performed at 5 time points over a 4-hour interval (0, 1, 2, 3, and 4 hours, within ±15 minutes of the scheduled time point).

n: On treatment day (Visit 8), IPS-EEG assessment will be performed predose (approximately within 30 minutes to 2 hours), and at 1, 2, 4, 6, and 8 hours postdose (a window of ±15 minutes is allowed at each postdose timepoint).

o: BL-VAS will be performed from each subject on each treatment day predose (within 2 hours) and at 1, 2, 4, 6, and 8 hours postdose.

p: C-SSRS will be performed at Screening, during each Treatment Visit (recommended to administer C-SSRS predose to ensure there is no increased risk of suicidality since last visit), and at the Follow-up/Early Discontinuation Visit.

Table 6 presents the blood sampling schedule for pharmacokinetic assessments, in addition for window periods for study assessments on Treatment visits (ie, Visit 2, Visit 3, Visit 4, Visit 5, and, as applicable Visit 8).

Table 6 Time Windows for Study Assessments on Treatment Days (Revised per Amendment 01)

Visit (Window)	Time Relative to the Administration	Acceptable Time Window
PK		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days) Visit 8 (±3 days)	Predose	–2 hours
	1, 2 hours	±10 minutes
	4, 6, and 8 hours	±15 minutes
Vital Signs		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days) Visit 8 (±3 days)	Predose	–2 hours
	1, 2, 4, 6, and 8 hours	±15 minutes
ECG		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days) Visit 8 (±3 days)	Predose	–2 hours
	4 hours	±30 minutes
Clinical Laboratory Tests		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days) Visit 8 (±3 days)	Predose	–2 hours to -30 minutes (before light snack)
IPS-EEG Assessment		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days) Visit 8 (±3 days)	Predose	-2 hours to -30 minutes
	1, 2, 4, 6, and 8 hours	±15 minutes

IPS-EEG = intermittent photic stimulation electroencephalogram, PK = pharmacokinetics

9.5.2.2 Description of Procedures/Assessments Schedule

The scheduling of study procedures and assessments are shown in Table 4 and 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, CNS-related side effects (eg, somnolence, body sway, dizziness and sedation) known to be associated with AMPA receptor antagonism will also be assessed using BL-VAS (Bond A, 1974). As BL-VAS measures effects of E2082 that are related to the underlying pharmacological activities of AMPA receptor antagonist, these measurements also serve as PD markers in this study.

The IPS-EEG procedure during this study will be performed based upon the protocol of Kastelejin et al (Kasteleijn-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 IPS-EEG 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 (ie, Follow-up/Early Discontinuation visit) and for 28 days after the last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

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

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

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

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 early after having been exposed to study drug are to complete the

study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 4 and Table 6). Early Discontinuation visit is not required for subjects who discontinued from the study before receiving the first study drug administration.

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. Data will be unblinded once double-blind treatment period has completed. Two sets of analyses tables will be created: one set after the unblinding using all the available data until that point and another set after all the subjects have completed the last study visit.

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 during each Treatment Period. A diminution in response is anticipated with the dose range. .

The primary endpoint, the mean change from baseline of the average PPR in the most sensitive is analyzed using a mixed effects model for crossover part of the study and summarized for each E2082 dose level and placebo regardless of crossover design. Another endpoint will include proportions of subjects with complete suppression, partial response, or no response

Complete suppression is defined as an SPR reduction to 0 over at least 1 time point for all 3 eye conditions. Partial response is defined as a reduction in SPR of at least 3 units from baseline for at least 3 time points, and no time points with at least 3 units of increase, in the most sensitive eye condition; without meeting the complete suppression definition. The definition of no response is as follows: Did not meet complete suppression or partial response definitions.

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.

9.7.1.1.2 SECONDARY ENDPOINTS

- Mean change from baseline in the PPR range in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- Onset, maximum change, and duration of response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- Frequency and percentage of subjects with complete suppression, partial response, and no response of SPR
- Changes from baseline in BL-VAS
- Incidence of TEAEs
- Clinically significant changes from baseline in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2082, compared to placebo
- PK parameters of E2082 (C_{max}, t_{max}, area under concentration-time curve from time 0 to 8 hours postdose [$AUC_{(0\text{-}8h)}$])

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Relationship between plasma exposure of E2082 (PK) and PD response (eg, onset, maximum change, and duration of photosensitivity response, BL-VAS)

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 PK 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 PD 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 E2082 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, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The Safety Analysis Set will be used for listings of individual E2082 plasma concentrations. The PK analysis set will be used for summaries of plasma E2082 concentrations and for analyses, 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 E2082. These parameters will include, but are not limited to:

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

The PK of E2082 will be analyzed based on available data from this study. The PK and PD Analysis Sets will be used to evaluate the relationship of PK of E2082 and change in SPR response. The PK-PD analyses may include the examination of the relationship of PK of E2082 and SPR (eg, time of onset, maximum change, and duration of response; and BL-VAS data) using model-based approaches, data permitting. Details of the PK/PD analyses will be described in a separately prepared analysis plan and its report.

Analysis variables: Plasma concentrations of E2082

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

Analysis methods: The PK of E2082 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, PHARMACOGENOMIC, AND OTHER BIOMARKER 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 in the most sensitive and 3 eye conditions will be analyzed using a mixed effects model for the crossover part of the study and summarized for each E2082 dose level and placebo regardless of crossover design. The mixed effects model for the crossover part of the study will include treatment (E2082 2.5 mg, 25 mg, and placebo), 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 E2082 dose (2.5 mg or 25 mg) compared to placebo, and 90% CIs will be presented with no adjustments for multiplicity.

Additional analysis by graphical exploration for the evaluation of onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions for each treatment. Similarly, frequency and percentage of subjects with complete suppression, partial suppression, and no response at each dose level of E2082 will be summarized descriptively and graphically for each treatment.

Sensitivity analyses may be conducted for photosensitivity response, for example, in subjects who completed all 3 Treatment Periods 1 through 3 versus those who are included in the PD Analysis Set. Other exploratory analyses may be conducted as data permit.

All other PD data (ie, BL-VAS data) 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.

PK-PD analyses may include the examination of the relationship of PK of E2082 and SPR (eg, time of onset, maximum change, and duration of response; and BL-VAS data) using model-based approaches, data permitting. Details of the PK/PD analyses will be described in a separately prepared analysis plan and its report.

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. 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, heart rate, 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 QTcF during the Treatment Period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

- For the QT interval assessment, clinically abnormal ECG results for QT interval corrected for heart rate using 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.

Upon consultation with the sponsor, subjects who discontinue from the study early may be replaced.

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

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

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

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB, but the health or regulatory authority and IRB 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, computed tomography [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 IB, 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 PI (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;

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				seizures
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

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

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2082-A001-201

Study Protocol Title: A Multicenter, Double-Blind, Randomized, Crossover, Single-Dose Study with An Open-Label Treatment Period Evaluating Pharmacodynamic Activity of E2082 in Adult Subjects with Photosensitive Epilepsy

Investigational Product Name: E2082

IND Number: 134556

SIGNATURES

Authors:

PPD
PPD
NBG
Eisai, Inc. Date

PPD
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NBG
Eisai, Inc. Date

PPD
PPD
NBG
Eisai, Inc. Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2082-A001-201
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Crossover, Single-Dose Study with An Open-Label Treatment Period Evaluating Pharmacodynamic Activity of E2082 in Adult Subjects with Photosensitive Epilepsy
Investigational Product Name:	E2082
IND Number:	134556

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:	E2082-A001-201
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Crossover, Single-Dose Study with An Open-Label Treatment Period Evaluating Pharmacodynamic Activity of E2082 in Adult Subjects with Photosensitive Epilepsy
Sponsor:	Eisai Inc. 100 Tice Boulevard, Woodcliff Lake, New Jersey 07677, US
Investigational Product Name:	E2082
Indication:	Not applicable
Phase:	2
Approval Date:	V1.0 21 Aug 2018 (original protocol)
IND Number:	134556
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.: E2082

Name of Active Ingredient: 2-Fluoro-6-[3-fluoro-8-oxo-7-(pyridin-3-yl)-7,8-dihydro-6*H*-pyrano[3,2-*b*:5,4-*b'*]dipyridin-9-yl]benzonitrile

Study Protocol Title

A Multicenter, Double-Blind, Randomized, Crossover, Single-Dose Study with An Open-Label Treatment Period Evaluating Pharmacodynamic Activity of E2082 in Adult Subjects with Photosensitive Epilepsy

Principal Investigator

Gregory Krauss, MD

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 8 to 9 months.

Phase 2

Objectives

Primary Objective

- To assess pharmacodynamic (PD) activity of E2082 as measured by suppression of epileptic photoparoxysmal response (PPR) in the subject's most sensitive eye condition in the photosensitivity model as a proof of principle of efficacy in subjects with photosensitive epilepsy, compared to placebo

Secondary Objectives

- To assess the PD activity of E2082 as measured by suppression of PPR in each of the 3 eye conditions (eye closure, eyes closed, and eyes open), compared to placebo
- To assess PD activity of E2082 as measured by onset, maximum change, and duration of photosensitivity response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- To assess proportion of subjects with complete suppression, partial suppression, and no response of standardized photosensitivity response (SPR)
- To assess other central nervous system (CNS)-related effects of E2082 based on Bond-Lader Visual Analogue Scale (BL-VAS)
- To assess the safety and tolerability of E2082 following single oral dose administration
- To assess the pharmacokinetics (PK) of E2082 following single oral dose administration

Exploratory Objective

- To explore relationships between PK and PD

Study Design

This is a multicenter, double-blind, randomized, 6-sequence, 3-treatment, 3-period, crossover study with an Open-Label Treatment Period, in adult subjects with photosensitive epilepsy. This study will use the photosensitivity proof of principle model to determine the potential of E2082 to reduce the photosensitive range in adult subjects.

This study will have 2 phases: Pretreatment Phase and Treatment Phase. The Pretreatment Phase will consist of a Screening Period (up to 3 weeks from Visit 1), during which each subject's study eligibility will be determined. The Treatment Phase will consist of 3 blinded Treatment Periods for a randomized crossover design, followed by an Open-label Treatment Period. During the Randomized Crossover Treatment Periods, there will be 3 Treatment Visits (Visit 2 [Treatment Period 1], Visit 3 [Treatment Period 2], and Visit 4 [Treatment Period 3]) evaluating single-dose administrations of either placebo, E2082 2.5 mg, or E2082 25 mg in a blinded manner. During the Open-label Treatment Period, there will be 1 treatment visit (Visit 5 [Treatment Period 4]) evaluating single-dose administration of E2082 40 mg. Treatment visits (ie, Visit 2, Visit 3, Visit 4, and Visit 5) will each be separated by a 2-week (±3 days) washout interval for a total of approximately 6 weeks, which will then be followed by a Follow-up Period of 2 weeks (±3 days) after the last day of study product administration. The anticipated study participation duration for each subject is approximately 11 weeks. All visits will be conducted on an outpatient basis.

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 meeting all eligibility criteria will enter into the Treatment Phase and be randomly assigned to 1 of 6 treatment sequences to receive, in a blinded fashion, a single oral dose of placebo control, E2082 2.5 mg, or E2082 25 mg during the Randomized Crossover Treatment Periods. This is followed by the Open-Label Treatment Period, during which each subject will receive a single dose of E2082 40 mg.

On the day of each Treatment Visit (ie, Visit 2, Visit 3, Visit 4, and Visit 5), subjects will arrive at the clinic in the morning following an overnight fast of at least 8 hours. Baseline intermittent photic stimulation (IPS)-electroencephalogram (EEG) assessments will be conducted 30 minutes to 2 hours before study product administration on each treatment day, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency for each eye condition.

After completion of the Open-label Treatment Period, subjects will enter the Follow-up Period, during which they will be required to complete a Follow-up visit (Visit 6) at 2 weeks ±3 days following the last day of study product administration.

Subjects who discontinue early from the study for any reason after having been exposed to study drug will undergo an Early Discontinuation Visit within 2 weeks ±3 days of their last dose of study drug. Early Discontinuation visit is not required for subjects who discontinued from the study before receiving the first study drug administration. Upon consultation with the sponsor, subjects who discontinue from the study early may be replaced.

The end of study is defined as the last subject completing the Follow-up Visit.

<u>IPS-EEG specific Subject Withdrawal/Stopping Criteria</u>

At the discretion of the investigator, a subject may be withheld from further IPS-EEG testing during a study visit or withdrawn from the study if any of the following 3 circumstances occur:

1. If a subject experiences:

   a) generalized tonic-clonic seizure (GTCS) on any study day, and the subject has not had a GTCS in the 6 months before enrollment, that subject will be discontinued from the study.

OR

b) GTCS during photic stimulation, 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, that subject will be discontinued from the study.
   Proconvulsive activity is defined as:

   a) 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; or

   b) change in the usual pattern of PPR that is typical for the subject such as: decrease in time to occurrence of PPRs at the same flash frequency; increase in the duration of the PPR; or, clear increase of PPR-related negative sensations (clinical signs) or appearance or increase of spontaneous epileptiform activity.
3. If a subject has widening of the photosensitivity range (becomes more sensitive) by more than 3 points on 2 consecutive occasions after dosing compared to Screening, the IPS will be terminated and the subject will not be permitted to participate in further IPS-EEG testing on the same day.

Number of Subjects

Approximately 9 subjects will be randomized to achieve 6 evaluable subjects.

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/or history of a PPR on EEG (ie, photosensitivity epilepsy).
3. If currently being treated with antiepileptic drugs (AEDs), up to a maximum of 3 concomitant AEDs is allowed provided that doses must have remained stable for at least 4 weeks before Screening. In the case where a new AED regimen has been initiated for a subject, the dose must be stable for at least 8 weeks before Screening. (See Exclusion Criteria #17-22 for AEDs that are exclusionary.)
4. Reproducible IPS-induced PPR on EEG of at least 3 points on the SPR scale in at least 1 eye condition (eye closure, eyes closed, eyes open) on at least 3 of the EEGs performed at Screening.
5. Body mass index (BMI) between 18 to 35 kg/m^2 (inclusive) and a total body weight greater than or equal to 45 kg at Screening.
6. Agrees to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period before 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 [β-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of β-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 before Screening.
6. Ongoing or history of GTCS within 6 months before Screening.
7. Subject who had developed a clinical seizure during previous PPR assessment, or who experiences a clinical seizure during the Screening IPS procedure.
8. Frequent spontaneous background burst or current evidence of proconvulsive activity on EEG (eg, increase in spike-wave activity) at Screening.
9. Inability to follow restriction on watching television, or use of any device(s) with an animated screen (eg, computer, video games, tablets, or smart phone) from the time of arrival at the study center until study procedures are completed for that day.
10. Currently active 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. 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 using Fridericia formula (QTcF) interval; or prolonged QT/QTcF interval (QTcF >450 msec) demonstrated on ECG at Screening or Baseline (based on average of triplicate ECGs).
12. Presence of 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.
13. Current/ongoing clinically significant active liver disease, porphyria, or with a family history

of severe hepatic dysfunction indicated by abnormal liver function tests (LFTs) greater than 3 times the upper limit of normal (ULN) (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).

14. Any history of gastrointestinal conditions or surgery that may affect PK profiles of E2082 (eg, hepatectomy, nephrectomy, and digestive organ resection).
15. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening.
16. Use of perampanel within 6 weeks before Screening.
17. Use of felbamate for less than 2 years or where the dose has not been stable for at least 8 weeks before Visit 1. Subject must not have a history of white blood cell (WBC) count below equal or less than 2500/μL (2.50 1E+09/L), platelet count below 100,000, LFTs above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If subjects received felbamate in the past, it must have been discontinued 8 weeks before Visit 1 to be eligible for study participation.
18. Use of vigabatrin within 5 months before Screening. Subjects who have discontinued vigabatrin for at least 5 months before Screening must have documentation showing no evidence of vigabatrin-associated clinically significant abnormality in a visual perimetry test in order to be eligible for the study.
19. Concomitant use of cannabinoids.
20. Use of benzodiazepines for epilepsy for which the dose has not been stable for greater than 4 weeks before Screening. Benzodiazepine use as rescue medication for seizure control is allowed; however, intermittent use of benzodiazepines for any other indication (eg, anxiety/sleep disorders) is prohibited.
21. Use of concomitant AEDs or other drugs that are known to be potent cytochrome P450 (CYP)3A enzyme inducers (such as carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, phenobarbital, and primidone) or CYP3A inhibitors within 4 weeks or 5 half-lives, whichever is longer.
22. Vagus nerve stimulation (VNS) implanted within 5 months or changes in parameter within 4 weeks before Screening.
23. On a ketogenic diet for which the diet is not a stable regimen for at least 4 weeks before Screening.
24. History of drug or alcohol dependency or abuse within the 12 months before Screening, or those subjects who have a positive drug test or alcohol test at Screening.
25. History of or ongoing multiple drug allergies or severe drug reaction to AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
26. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
27. 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 Columbia-Suicide Severity Rating Scale [C-SSRS]).
28. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS).
29. 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.
30. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5 half-lives, whichever is longer, preceding informed consent, except the investigational study for the evaluation of commercial IPS machine.

Study Treatments

Test Drug: E2082

E2082 will be supplied as 0.5-mg and 5-mg tablets for oral administration.

Comparator Drug: E2082-matched placebo

Randomized Crossover Treatment Periods

Each subject will receive a single oral dose of E2082 2.5 mg, E2082 25 mg, and matched-placebo in a cross-over sequence according to his/her randomization code.

Treatment A (Placebo): 5 x E2082-matched placebo tablets
Treatment B (E2082 2.5 mg): 5 x E2082 0.5-mg tablet
Treatment C (E2082 25 mg): 5 x E2082 5-mg tablets

Open-label Treatment Period

Each subject will receive a single oral dose of E2082 40 mg (8 x E2082 5-mg tablets).

All Study Drug 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 approximately 30 minutes predose (after clinical laboratory blood collection) and approximately 2 hours postdose. Water will be permitted ad libitum except from the time of dosing until 1 hour postdose.

Duration of Treatment

Single dose

(ie, the Treatment Phase will consist of 4 Treatment Periods each with a single dose administration)

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 before Screening. In the case where a new AED regimen has been initiated for a subject, the dose must be stable for at least 8 weeks before screening. During the study, changes to concomitant AEDs (including dosage) are not permitted unless medically necessary and upon consultation with the Sponsor.

Use of the following AEDs during the course of the study is not allowed:

- Perampanel
- Vigabatrin
- Cannabinoids
- Benzodiazepines for non-epilepsy indications (eg, anxiety/sleep disorders)
- Enzyme-inducing antiepileptic drugs (EIAEDs, eg, carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, phenobarbital, and primidone)

Concomitant use of medications known to be potent CYP3A inducers/inhibitors including, but not limited to, rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, modafinil, pioglitazone, and rifabutin will not be permitted and are to be discontinued within 28 days before Visit 1.

Vagus nerve stimulation (VNS) is not considered as one of the 3 allowed concomitant AEDs. However, VNS implantation during the course of the study is prohibited. For subjects who have VNS implanted before participation in this study, changes to VNS parameters are not allowed unless medically necessary.

Changes to ketogenic diet (eg, median chain triglyceride level) are not allowed during the study.

Assessments

Efficacy Assessments

Not applicable.

Pharmacokinetic Assessments

On each treatment day, blood samples for the determination of plasma concentrations of E2082 will be collected from each subject predose (within 2 hours), and at 1 (±10 min), 2 (±10 min), 4 (±15 min), 6 (±15 min), and 8 (±15 min) hours postdose.

Pharmacodynamic Assessments

IPS-EEG

PD activity of E2082 will be assessed by suppression of PPR following IPS using the Grass PS 33 photic stimulator with an unpatterned glass lamp and an intensity of 100 cd/m^2/flash. Each IPS-EEG assessment will be conducted in all 3 eye conditions (eye closure, eyes closed, and eyes open; each for a minimum of 2.5 minutes) at ascending and then descending photo stimulation frequencies. The lower and upper limit of photosensitivity to IPS threshold frequency will be determined for each eye condition. PPR is expected to be within the range of 2 Hz to 60 Hz, depending on the subject's sensitivity to IPS. Qualified medical personnel for the management of acute seizures will be present during the day of IPS-EEG procedure throughout the study.

During the Screening Visit (Visit 1), IPS-EEG assessment will be performed at 5 time points, over a 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. However, the final determination of study eligibility will include predose assessments when the subject returns to study site for Visit 2. On each treatment day (ie, Visit 2, Visit 3, Visit 4, and Visit 5), IPS-EEG assessments will be conducted predose (approximately 30 minutes to 2 hours), and at 1, 2, 4, 6, and 8 hours (within ±15 minutes of each scheduled time point) postdose to characterize the time course of E2082 PD activity including the onset, maximum change from baseline, and duration of the reduction in PPR response. The predose assessment serves as the baseline on each treatment day.

Other PD assessments

The BL-VAS (Bond A, 1974) for CNS-related effects of E2082 (such as somnolence, sedation, dizziness, and body sway) for potential sedative effects of E2082 will be evaluated for each subject on each treatment day predose (within 2 hours) and at 1, 2, 4, 6, and 8 hour postdose.

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

Pharmacogenomic and Other Biomarker Assessments

Not applicable.

Safety Assessments

Safety will be assessed by monitoring and recording all adverse events (AEs). Additionally, safety assessments will consist of physical and neurological examinations, vital signs, 12-lead ECG, clinical laboratory test (hematology, blood chemistry, and urinalysis), and (for women of childbearing potential only) pregnancy test. A full neurological examination will be conducted during the Screening Visit. An abbreviated neurological examination will be performed on each treatment day (predose and at 4 hours postdose), and during Follow-up/Early Discontinuation visit.

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

Other Assessments

Not applicable.

Bioanalytical Methods

Plasma concentrations of E2082 will be measured using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method.

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

Secondary Endpoints

- Mean change from baseline in the PPR range in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- Onset, maximum change, and duration of response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- Frequency and percentage of subjects with complete suppression, partial response, and no response of SPR
- Changes from baseline in BL-VAS
- Incidence of treatment-emergent adverse events (TEAEs)
- Clinically significant changes from baseline in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2082, compared to placebo
- PK parameters of E2082 (C_{max}, time to reach C_{max} following drug administration [t_{max}], area under concentration-time curve from time 0 to 8 hours postdose [$AUC_{(0-8h)}$])

Exploratory Endpoints

- Relationship between plasma exposure of E2082 (PK) and PD response (eg, onset, maximum change, and duration of photosensitivity response, BL-VAS)

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 PK 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 PD 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, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

The Safety Analysis Set will be used for listings of individual E2082 plasma concentrations. The PK

analysis set will be used for summaries of plasma E2082 concentrations and for analyses, 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 E2082. 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 E2082 will be analyzed based on available data from this study. The PK and PD Analysis Sets will be used to evaluate the relationship of PK of E2082 and change in SPR response. PK-PD analyses may include the examination of the relationship of PK of E2082 and SPR (eg, time of onset, maximum change, and duration of response; and BL-VAS data) using model-based approaches, data permitting. Details of the PK/PD analyses will be described in a separately prepared analysis plan and its report.

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 in the most sensitive and 3 eye conditions will be analyzed using a mixed effects model for the crossover part of the study and summarized for each E2082 dose level and placebo regardless of crossover design. The mixed effects model for the crossover part of the study will include treatment (E2082 2.5 mg, 25 mg, and placebo), 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 E2082 dose (2.5 mg or 25 mg) compared to placebo, and 90% CIs will be presented with no adjustments for multiplicity.

Additional analysis by graphical exploration for the evaluation of onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions for each treatment. Similarly, frequency and percentage of subjects with complete suppression, partial suppression, and no response at each dose level of E2082 will be summarized descriptively and graphically for each treatment.

Sensitivity analyses may be conducted for photosensitivity response, for example, in subjects who completed all 3 Treatment Periods 1 through 3 versus those who are included in the PD Analysis Set. Other exploratory analyses may be conducted as data permit.

All other PD data (ie, BL-VAS) 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.

Pharmacogenomic and Other Biomarker Analyses

Not applicable.

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. 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
AMPA	α amino 3 hydroxy-5-methyl-4-isoxazolepropionic acid
AST	aspartate aminotransferase
$AUC_{(0\text{-}8h)}$	area under concentration-time curve from time 0 to 8 hours postdose
β-hCG	beta-human chorionic gonadotropin
BL	Bond-Lader
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
CYP	cytochrome P450
EEG	electroencephalogram
GTCS	generalized tonic-clonic seizure
hCG	human chorionic gonadotropin
IB	Investigator's Brochure
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
LFT	liver function test
LNH	low/normal/high
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetics
POC	proof-of-concept

Abbreviation	Term
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_{max}	time at which the highest drug concentration occurs (time to reach C_{max} following drug administration)
ULN	upper limit of normal
WBC	white blood cell
VAS	Visual Analogue Scale
VNS	vagus nerve stimulation

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/she 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 study is defined as the last subject completing the Follow-up Visit. 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 CFR (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.

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 overall development plan of E2082 will be based on the potential role of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist as an antiepileptogenesis agent in a number of neurological disorders associated with glutamate-mediated neuronal overexcitation.

7.1.1 Mechanism of Action – E2082

E2082 is a selective noncompetitive AMPA type glutamate receptor antagonist. AMPA receptors, located on post-synaptic neurons, are responsible for fast glutamate-mediated excitation at synapses. Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS) and is implicated in a number of neurological disorders caused by neuronal overexcitation.

E2082 demonstrated potent in vitro inhibitory effect (AMPA receptor functional assay) and in vivo antiseizure effect in various animal models of epilepsy (audiogenic seizure, maximal electroshock [MES] seizure, and pharmacoresistant 6 Hz psychomotor seizure mouse models). Preclinical evidence suggests that E2082 showed a broad window between therapeutic effect and AMPA receptor antagonism-related CNS side effects (eg, sedation, ataxia) with a protective index (TD_{50} [rotarod test]/antiseizure ED_{50}) of 3.2- to 20-fold. Refer to the Investigator's Brochure (IB) for detailed information.

7.1.2 Clinical Experience With E2082

E2082 is currently under Phase 1 clinical development that comprises the first-in-human, double-blind, placebo-controlled, single- and multiple-ascending dose (SAD-MAD) study (E2082-J081-001; Study 001) in healthy male subjects in Japan. The SAD portion of Study 001 (Part A) evaluated pharmacokinetics (PK), safety and tolerability of E2082 in healthy male adult subjects at doses of 0.2, 0.5, 1, 2.5, 5, 10, 15, 25, and 40 mg under fasted condition, as well as at 5 mg under fed condition, and in elderly subjects at 10 mg. E2082 was administered as oral tablets (0.5 or 5-mg dose strengths) in all dose cohorts, except for the 0.2-mg cohort (as oral solution). The SAD portion of Study 001 is completed, in which a total of 60 subjects received a single dose of E2082 (0.2 through 40 mg) and 20 subjects received placebo. The MAD portion of Study 001 is ongoing.

7.1.2.1 Pharmacokinetics

Preliminary PK data suggest that E2082 was rapidly absorbed with median time to maximum plasma concentration (t_{max}) observed approximately 1 to 4 hours following oral administration of E2082 tablets over the dose range of 0.5 to 40 mg. The average half life of E2082 was approximately 30 hours. The mean plasma exposure (peak plasma concentration [C_{max}] and area under the plasma concentration-time curve from zero time extrapolated to infinite time [$AUC_{(0\text{-inf})}$]) increased approximately dose proportionally with increasing dose across the dose

range of 0.5 to 40 mg. Food intake did not appear to affect the rate or extent of E2082 absorption. Refer to the IB for a full description of PK.

7.1.2.2 Pharmacodynamics

Saccadic eye movements was included in Study 001 for evaluation of potential CNS-related side effects of E2082 as an exploratory pharmacodynamic (PD) parameter. Preliminary results suggest a dose/concentration-dependent reduction in peak saccadic velocity following single dose administration of E2082. Refer to the IB for detailed information.

7.1.2.3 Safety and Tolerability

Preliminary safety data from Study 001 showed that E2082 was well-tolerated following single oral dose administration in healthy subjects. There were no deaths, serious adverse events (SAEs), or adverse events leading to discontinuation, and no medically significant findings from laboratory tests, ECG, or vital signs. A total of 16 subjects experienced treatment-emergent adverse events (TEAEs); 15/60 (25%) subjects receiving E2082 and 1/20 (5%) in the placebo group. The most common TEAEs reported were dizziness (14/60 [23.3%] subjects) and somnolence (6/60 [10.0%] subjects), followed by nausea (2/60 [3.3%] subjects), decreased appetite (2/60 [3.3%] subjects), back pain (1/60 [1.7%] subjects), and nasopharyngitis (1/20 [5.0%] subjects). All TEAEs were deemed related to E2082, except for back pain and nasopharyngitis. All TEAEs reported were mild to moderate in severity, and all resolved without any medical interventions.

Please refer to IB for a full summary of TEAEs, including safety and tolerability information.

7.2 Study Rationale

7.2.1 Photosensitivity Proof-of-Concept Model

Patients with epilepsy often have intermittent seizures that occur at variable times. Consequently, studies evaluating new antiseizure medications require that large numbers of subjects be evaluated over several months of treatment to accurately assess treatment effects. In such circumstances, it is extremely useful to conduct a “proof-of-concept” (POC) study, which would screen potential antiseizure agents for possible efficacy before proceeding to lengthy and expensive studies that expose many subjects to a new compound. The photosensitivity POC study design has been used successfully to evaluate potential antiseizure effects of new agents in early stage development in small groups of subjects with photically-induced generalized epileptiform responses on electroencephalogram (EEG), called photoparoxysmal responses (PPRs).

Photosensitivity describes the ability to produce epileptiform activities in response to intermittent photic stimulation. This EEG pattern is called PPR. Some subjects who are photosensitive have photosensitive epilepsy, and may have clinical events in response to photic stimulation. This response is also characterized as “reflex epilepsy” in the small group of subjects with epilepsy

who have seizures in response to photic stimulation in the absence of adequate treatment. Many other subjects will have PPR demonstrated only as an EEG pattern. Photosensitivity is typically a genetic trait with a Mendelian autosomal dominant pattern. When associated with epilepsy, the epilepsy type will almost always be classified as generalized idiopathic epilepsy, and the clinical seizure semiology will be characterized by absence, generalized tonic-clonic, or myoclonic seizures. Any of these 3 generalized seizure types can be precipitated by photic stimulation.

In the photosensitivity study design model, subjects who have PPR in response to flickering diffuse white light are included. A photosensitivity range for each subject can be determined by eliciting the upper and lower limits of sensitivity to intermittent photic stimulation (IPS) in order not to evoke seizures for that particular subject. Subjects are usually sensitive to IPS within clearly defined limits of flash frequency (mostly between 10-30 Hz). The photosensitivity range is relatively stable over time for each subject, although it can decrease or be eliminated by the use of AEDs.

This photosensitivity range, defined as the difference between the highest and lowest flash rates that consistently elicit a PPR, can be used as a quantitative measure of photosensitivity and, therefore, epileptogenicity. In photosensitivity studies, a stable baseline is defined as the baseline at the Screening and Predose on the day of each Treatment Period. Usually during a photosensitivity study, the baseline is stable throughout the study. The photosensitivity range is measured repeatedly (up to 8 times) over the course of a single day, and the range can be measured rapidly (over a 5-minute interval) in an EEG laboratory. Reduction in the photosensitivity range can then be easily quantified after a single dose of an AED. This reduction has been used to demonstrate an antiepileptic effect for a number of AEDs currently marketed or in development, most notably valproate, levetiracetam, lamotrigine, brivaracetam, carisbamate, JZP4 (Jazz Pharmaceuticals), cenobamate (YKP3089, SK Life Sciences), and selurampanel (BGG492, Novartis). This POC model has been successful in identifying multiple drugs in early phase drug development that were subsequently effective in large clinical studies (Binnie, et al., 1986a; Binnie, et al., 1986b; Binnie, 1988; Kasteleijn-Nolst Trenité, et al., 1996; Kasteleijn-Nolst Trenité, et al., 2007; Trenité, et al., 2007; French and Krauss, 2014; Kasteleijn-Nolst Trenité, et al., 2015).

The intent of this study is to provide a POC signal and evidence of a dose-response relationship, and to inform the design and dose selection for Phase 2 of the clinical development program.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to assess PD activity of E2082 as measured by suppression of epileptic PPR in the subject's most sensitive eye condition in the photosensitivity model as a proof of principle of efficacy in subjects with photosensitive epilepsy, compared to placebo.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the PD activity of E2082 as measured by suppression of PPR in each of the 3 eye conditions (eye closure, eyes closed, and eyes open), compared to placebo
- To assess PD activity of E2082 as measured by onset, maximum change, and duration of photosensitivity response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- To assess proportion of subjects with complete suppression, partial suppression, and no response of standardized photosensitivity response (SPR)
- To assess other CNS-related effects of E2082 based on Bond-Lader Visual Analogue Scale (BL-VAS)
- To assess the safety and tolerability of E2082 following single oral dose administration
- To assess the PK of E2082 following single oral dose administration

8.3 Exploratory Objective

- To explore relationships between PK and PD

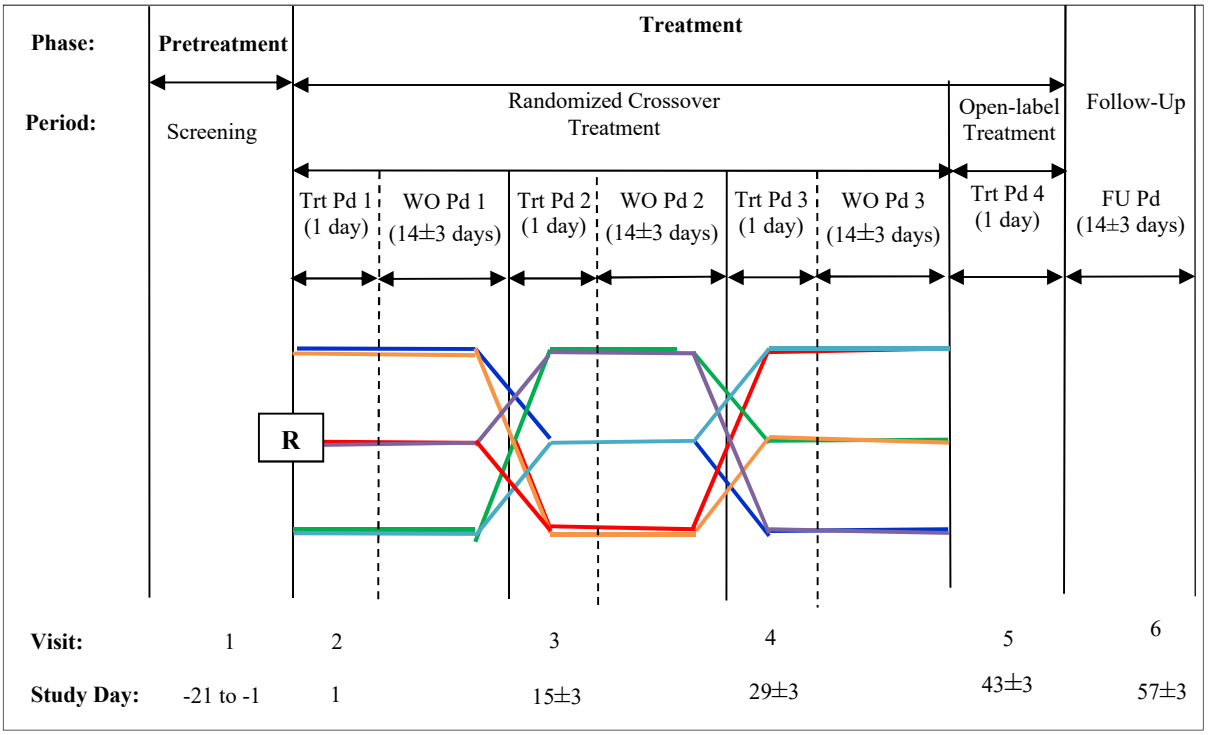
9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, double-blind, randomized, 6-sequence, 3-treatment, 3-period, crossover study with an Open-label Treatment Period, in adult subjects with photosensitive epilepsy. This study will use the photosensitivity proof of principle model to determine the potential of E2082 to reduce the photosensitive range in adult subjects.

This study will have 2 phases: Pretreatment Phase and Treatment Phase. The Pretreatment Phase will consist of a Screening Period (up to 3 weeks from Visit 1), during which each subject's study eligibility will be determined. The Treatment Phase will consist of 3 blinded Treatment Periods for a randomized crossover design, followed by an Open-label Treatment Period. During the Randomized Crossover Treatment Periods, there will be 3 Treatment Visits (Visit 2 [Treatment Period 1], Visit 3 [Treatment Period 2], and Visit 4 [Treatment Period 3]) evaluating single-dose administrations of either placebo, E2082 2.5 mg, or E2082 25 mg in a blinded manner. During the Open-label Treatment Period, there will be 1 treatment visit (Visit 5 [Treatment Period 4]) evaluating single-dose administration of E2082 40 mg. Treatment visits (ie, Visit 2, Visit 3, Visit 4, and Visit 5) will each be separated by a 2-week (±3 days) washout interval for a total of approximately 6 weeks, which will then be followed by a Follow-up Period of 2 weeks (±3 days) after the last day of study product administration. The anticipated study participation duration for each subject is approximately 11 weeks. All visits will be conducted on an outpatient basis.

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



Note: FU visit is a single visit at the end of the Follow-up Period.
FU = Follow-up, Pd = Period, R = Randomization, Trt = Treatment, WO = Washout.

Figure 1 Study Design for Study E2082-A001-201

9.1.1 Pretreatment Phase

The Pretreatment Phase will consist of a Screening Period (up to 3 weeks from Visit 1), during which each subject's study eligibility will be determined.

9.1.1.1 Screening Period

Screening will occur between Day –21 and Day –1. The purpose of the Screening Period is to establish protocol eligibility. Signed informed consent must be obtained before any study procedures (including screening procedures) can be conducted. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a diagnosis and/or history of a PPR on EEG (ie, photosensitive epilepsy) for which they may receive up to 3 concomitant AEDs (Section 9.4.7).

At the Screening Visit (Visit 1), subjects will undergo an IPS-EEG assessment in 3 eye conditions (eye closure, eyes closed, and eyes open) at ascending and then descending photo-stimulation frequencies. At the Screening Visit, each frequency will be assessed in 3 eye conditions (eye closure, eyes closed, and eyes open) commencing at 2 Hz. As soon as generalized EEG epileptiform activity appears, the stimulation for that particular frequency in that particular eye condition will be instantly terminated. For the other eye conditions, ascending frequencies will be used, until generalized epileptiform activity is seen. This procedure will

determine the lower threshold frequencies for each eye condition. Similar assessments will then be carried out starting at 60 Hz and descending through the standard frequencies. To avoid occurrence of a seizure, the stimulator will be turned off immediately if a generalized response is observed, and the sequence will be stopped at that point in that specific eye condition. In this manner, for each eye condition, the upper threshold frequencies are determined.

During the Screening Visit (Visit 1), IPS-EEG assessment will be performed at 5 time points, over a 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. However, the final determination of study eligibility will include predose assessments when the subject returns to study site for Visit 2. The Screening assessments will be conducted, including determination of the lower and upper limit of photosensitivity to IPS-EEG threshold frequency for each eye condition. Qualified medical personnel for the management of acute seizures will be present during the day of IPS-EEG procedure throughout the study.

Upon review by the investigator, subjects whose Screening assessments (including Day 1 [Visit 2] predose procedures) continue to meet all of the inclusion/exclusion criteria will enter the Treatment Phase.

9.1.2 Treatment Phase

The duration of the Treatment Phase will be 6 weeks and will include 3 blinded Treatment Periods for a randomized crossover design, followed by an Open-label Treatment Period.

Up to 3 concomitant AEDs (Section 9.4.7) are allowed during the course of the study, provided that the dosage of concomitant AED(s) has remained stable for at least 4 weeks before Screening. In the case where a new AED regimen has been initiated for a subject, the dose must be stable for at least 8 weeks before screening. During the study, changes to concomitant AEDs (including dosage) are not permitted unless medically necessary and upon consultation with the Sponsor. Adherence to a stable AED regimen is critical as missed doses or changes during the study may affect the subject's photosensitivity response.

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.

9.1.2.1 Randomized Crossover Treatment Periods (Treatment Periods 1 to 3)

During the Randomized Crossover Treatment Periods, there will be 3 Treatment Visits (Visit 2 [Treatment Period 1], Visit 3 [Treatment Period 2], and Visit 4 [Treatment Period 3]) evaluating single-dose administrations of either placebo, E2082 2.5 mg, or E2082 25 mg. Subjects will be randomly assigned to 1 of 6 treatment sequences to receive the 3 treatments, in a blinded manner in a cross-over sequence according to his/her randomization code (Table 1).

Table 1 Treatment Sequences

Sequence	Treatment Period 1 (Visit 2)	Treatment Period 2 (Visit 3)	Treatment Period 3 (Visit 4)
1: ABC	Placebo	E2082 2.5 mg	E2082 25 mg
2: BCA	E2082 2.5 mg	E2082 25 mg	Placebo
3: CAB	E2082 25 mg	Placebo	E2082 2.5 mg
4: ACB	Placebo	E2082 25 mg	E2082 2.5 mg
5: BAC	E2082 2.5 mg	Placebo	E2082 25 mg
6: CBA	E2082 25 mg	E2082 2.5 mg	Placebo
A = Placebo; B = E2082 2.5 mg; C = E2082 25 mg			

On the day of each Treatment Visit (ie, Visit 2, Visit 3, and Visit 4), subjects will arrive at the clinic in the morning following an overnight fast of at least 8 hours. In order to enable discrimination between spontaneous and IPS evoked discharges, the subject will be assessed, at the start of each treatment day (ie, Visit 2, Visit 3, and Visit 4), for ≥2.5 minutes with each of the 3 eye conditions without any stimulation. Baseline IPS-EEG assessments will be conducted 30 minutes to 2 hours before study product administration on each treatment day, including determination of the lower and upper limit of photosensitivity to IPS threshold frequency for each eye condition. The predose assessment serves as the baseline on each treatment day. Trains of flashes at constant frequency will be delivered for 4 to 6 seconds. Intervals between successive flash trains at a given frequency will last for at least 5 seconds. Determination of the photosensitivity ranges will be assessed with separate trains of flashes of 4 to 6 seconds duration (or less if generalized epileptic activity occurs). Flashes will be administered at standard frequencies of 2, 5, 8, 10, 13, 15, 18, 20, 23, 25, 30, 40, 50, and 60 Hz. IPS-EEG assessments will be repeated at 1, 2, 4, 6, and 8 hours (within ±15 minutes of each scheduled time point) following study product administration. PK, PD (B-L VAS), and vital signs assessments will be conducted predose, and at the same postdose time points as IPS-EEG measurements. Other safety assessments will be performed on each treatment visit day either predose only (clinical laboratory tests, Columbia-Suicide Severity Rating Scale (C-SSRS), and urine pregnancy test [for women of childbearing potential only]), or both predose and at 4 hours postdose (brief neurological and 12-lead ECG examinations).

9.1.2.2 Open-label Treatment Period

There will be 1 treatment visit (Visit 5 [Treatment Period 4]) evaluating single-dose administration of E2082 40 mg.

Subjects will return to the study site after the 2-week [±3 days] washout interval following the Randomized Crossover Treatment Period 3 and will receive a single dose of 40 mg E2082. The same study procedures for Treatment Periods 1 through 3 (ie, Visit 2, Visit 3, and Visit 4) will apply to Treatment Period 4 (ie, Visit 5), except that study drug administration is not blinded.

Concomitant medication restrictions from the Randomized Crossover Treatment Period will apply to the Open-label Treatment Period.

9.1.3 Follow-Up Period

After completion of the Open-label Treatment period, subjects will enter the Follow-up Period, during which they will be required to complete a Follow-up visit (Visit 6) at 2 weeks ±3 days following the last day of study product administration.

At the end of the Follow-up Period, subjects will be required to complete a Follow-up visit.

9.2 Discussion of Study Design, Including Choice of Control Groups

Randomization will be used in this study in the Randomized Crossover Treatment Periods 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 of age at the time of informed consent.
2. A diagnosis and/or history of a PPR on EEG (ie, photosensitivity epilepsy).
3. If currently being treated with AED(s), up to a maximum of 3 concomitant AEDs is allowed provided that doses must have remained stable for at least 4 weeks before Screening. In the case where a new AED regimen has been initiated for a subject, the dose must be stable for at least 8 weeks before Screening. (See Exclusion Criteria #17-22 for AEDs that are exclusionary.)
4. Reproducible IPS-induced PPR on EEG of at least 3 points on the SPR scale in at least 1 eye condition (eye closure, eyes closed, eyes open) on at least 3 of the EEGs performed at Screening.
5. Body mass index (BMI) between 18 to 35 kg/m^2 (inclusive) and a total body weight greater than or equal to 45 kg at Screening.
6. Agrees to refrain from strenuous exercise and alcohol consumption during the 24-hour period before Screening and during the 24-hour period before 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 [β-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of β-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 before Screening.
6. Ongoing or history of generalized tonic-clonic seizures (GTCS) within 6 months before Screening.
7. Subject who had developed a clinical seizure during previous PPR assessment, or who experiences a clinical seizure during the Screening IPS procedure.

8. Frequent spontaneous background burst or current evidence of proconvulsive activity on EEG (eg, increase in spike-wave activity) at Screening.
9. Inability to follow restriction on watching television, or use of any device(s) with an animated screen (eg, computer, video games, tablets, or smart phone) from the time of arrival at the study center until study procedures are completed for that day.
10. Currently active 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. 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 using Fridericia formula (QTcF) interval; or prolonged QT/QTcF interval (QTcF >450 msec) demonstrated on ECG at Screening or Baseline (based on average of triplicate ECGs).
12. Presence of 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.
13. Current/ongoing clinically significant active liver disease, porphyria, or with a family history of severe hepatic dysfunction indicated by abnormal liver function tests (LFTs) greater than 3 times the upper limit of normal (ULN) (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).
14. Any history of gastrointestinal conditions or surgery that may affect PK profiles of E2082 (eg, hepatectomy, nephrectomy, and digestive organ resection).
15. Active viral hepatitis (B or C) as demonstrated by positive serology at Screening.
16. Use of perampanel within 6 weeks before Screening.
17. Use of felbamate for less than 2 years or where the dose has not been stable for at least 8 weeks before Visit 1. Subject must not have a history of white blood cell (WBC) count below equal or less than 2500/μL (2.50 1E+09/L), platelet count below 100,000, LFTs above 3 times the ULN, or other indication of hepatic or bone marrow dysfunction while receiving felbamate. If subjects received felbamate in the past, it must have been discontinued 8 weeks before Visit 1 to be eligible for study participation.
18. Use of vigabatrin within 5 months before Screening. Subjects who have discontinued vigabatrin for at least 5 months before Screening must have documentation showing no evidence of vigabatrin associated clinically significant abnormality in a visual perimetry test in order to be eligible for the study.
19. Concomitant use of cannabinoids.
20. Use of benzodiazepines for epilepsy for which the dose has not been stable for greater than 4 weeks before Screening. Benzodiazepine use as rescue medication for seizure control is allowed; however, intermittent use of benzodiazepines for any other indication (eg, anxiety/sleep disorders) is prohibited.
21. Use of concomitant AEDs or other drugs that are known to be potent cytochrome P450 (CYP)3A enzyme inducers (such as carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, phenobarbital, and primidone) or CYP3A inhibitors within 4 weeks or 5 half-lives, whichever is longer.

22. Vagus nerve stimulation (VNS) implanted within 5 months or changes in parameter within 4 weeks before Screening.
23. On a ketogenic diet for which the diet is not a stable regimen for at least 4 weeks before Screening.
24. History of drug or alcohol dependency or abuse within the 12 months before Screening, or those subjects who have a positive drug test or alcohol test at Screening.
25. History of or ongoing multiple drug allergies or severe drug reaction to AED(s), including dermatological (eg, Stevens-Johnson syndrome), hematological, or organ toxicity reactions.
26. Subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
27. 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).
28. Any lifetime suicidal behavior (per the Suicidal Behavior section of the C-SSRS).
29. 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.
30. Currently enrolled in another clinical study or used any investigational drug or device within 28 days or 5 half-lives, whichever is longer, preceding informed consent, except the investigational study for the evaluation of commercial IPS machine.

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.

Subjects who discontinue from the study early may be replaced upon consultation with the sponsor.

9.3.3.1 IPS-EEG-Specific Subject Withdrawal/Stopping 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.

At the discretion of the investigator, a subject may be withheld from further IPS-EEG testing during a study visit or withdrawn from the study if any of the following 3 circumstances occur:

1. If a subject experiences:

   a) GTCS on any study day, and the subject has not had a GTCS in the 6 months before enrollment, that subject will be discontinued from the study.

   OR

   b) GTCS during photic stimulation, 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, that

subject will be discontinued from the study.
Proconvulsive activity is defined as

a) 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; or

b) change in the usual pattern of PPR that is typical for the subject such as: decrease in time to occurrence of PPRs at the same flash frequency; increase in the duration of the PPR; or, clear increase of PPR-related negative sensations (clinical signs) or appearance or increase of spontaneous epileptiform activity.

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

9.4 Treatments

9.4.1 Treatments Administered

9.4.1.1 Randomized Crossover Treatment Periods

The following treatments will be administered as a single oral dose (Table 2). Each subject will receive each treatment in a sequence according to the randomization code (Table 1).

Table 2 Treatment Description

Treatment	Study Drug/Dose	Study Drug(s) to be Administered
A	Placebo	5 x E2082-matched placebo tablets
B	E2082 2.5 mg	5 x E2082 0.5-mg tablets
C	E2082 25 mg	5 x E2082 5-mg tablets

9.4.1.2 Open-label Treatment Period

Each subject will receive a single oral dose of E2082 40 mg (8 x E2082 5-mg tablets).

9.4.2 Identity of Investigational Products

E2082 film-coated tablets (0.5 mg and 5 mg) and corresponding placebo are yellowish red, approximately 5.1 mm in diameter. Test drug and placebo will be supplied by the sponsor in labeled containers.

9.4.2.1 Chemical Name, Structural Formula of E2082

- Test drug code: E2082
- Generic name: Not Applicable

- Chemical name: 2-Fluoro-6-[3-fluoro-8-oxo-7-(pyridin-3-yl)-7,8-dihydro-6*H*-pyrano[3,2-*b*:5,4-*b'*]dipyridin-9-yl]benzonitrile
- Molecular formula: $C_{23}H_{12}F_2N_4O_2$
- Molecular weight: 414.37

9.4.2.2 Comparator Drug

Placebo tablet with matching color and appearance to E2082 tablet will be supplied.

9.4.2.3 Labeling for Study Drug

E2082 will be labeled in accordance with text that is in full regulatory compliance.

9.4.2.4 Storage Conditions

E2082 will be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that E2082 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

9.4.3.1 Randomized Crossover Treatment Periods

Subjects will be assigned to all 3 treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent, unblinded, statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

9.4.3.2 Open-Label Treatment Period

Not applicable, as each subject will receive a single oral dose of E2082 40 mg (8 x E2082 5-mg tablets).

9.4.4 Selection of Doses in the Study

Single oral doses of 2.5 mg and 25 mg are currently being proposed for this study. A third dose of 40 mg, was selected as the highest dose in this photosensitivity study, and was determined following review of available PK/safety data from the 40-mg cohort in Study 001.

The low dose of 2.5 mg was selected based on the exposures observed at ED_{50} in preclinical mouse model (6 Hz psychomotor seizure model). Based on preliminary SAD PK data from Study 001, a single dose of 2.5 mg is expected to achieve plasma concentrations at or above the

predicted minimum effective plasma concentration of 80 ng/mL for approximately 8 hours in the majority of the subjects (Figure 2).

In the ongoing first-in-human study (Study 001), E2082 was well tolerated up to 40 mg (the highest dose level with PK and safety data evaluated). The proposed dose range between 2.5 mg and the highest dose of 40 mg are expected to provide a wide range of exposure (approximately 10- to 16-fold) to demonstrate POC and may also support exploratory PK/PD response analysis.

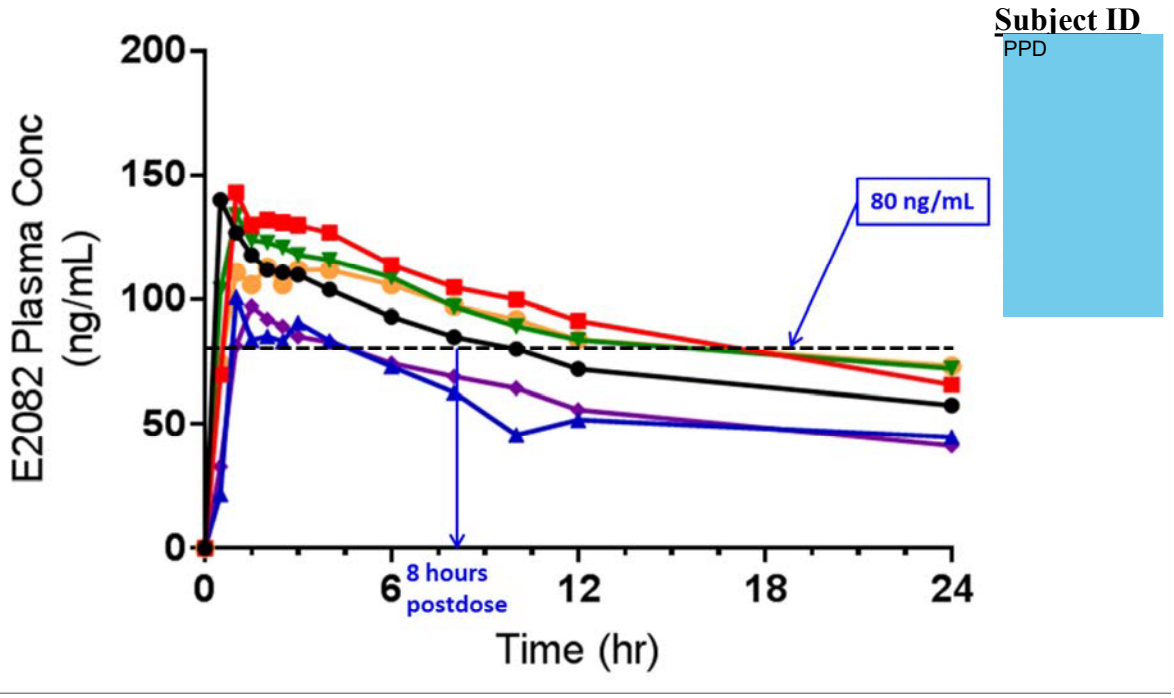


Figure 2 Individual plasma concentration-time profiles of E2082 (2.5 mg) following single oral dose administration in Study E2082-A001-001

conc = concentration

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, Visit 2, Visit 3, Visit 4, and Visit 5). A light snack can be provided at 30 minutes predose (after clinical laboratory blood collection) and at 2 hours postdose.

9.4.6 Blinding

Central EEG reading of all EEG records (including Screening and Treatment Periods 1 through 4) will be performed in a blinded and independent manner. Investigator(s) may consult with the central read only during the Pretreatment Phase, if needed, for IPS-EEG eligibility determination.

During the Randomized Crossover Treatment Periods, 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/designee (with the exception of the independent biostatistician and unblinded CRAs) 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 E2082 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 tablets 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 (see also Section 9.5.4.5). 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 within 3 months before the Screening Visit and throughout the course of 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 (with the exception of those AEDs listed in Section 9.4.7.1) are allowed during the course of the study, provided that the dosage of concomitant AED(s) has remained stable for at least 4 weeks before Screening. In the case where a new AED regimen has been initiated for a subject, the dose must be stable for at least 8 weeks before screening. During the study, changes to concomitant AEDs (including dosage) are not permitted unless medically necessary and upon consultation with the Sponsor.

Vagus nerve stimulation (VNS) is not considered as one of the 3 allowed concomitant AEDs. However, VNS implantation during the course of the study is prohibited. For subjects who have VNS implanted prior to participation in this study, changes to VNS parameters are not allowed unless medically necessary.

Likewise, ketogenic diet is not considered as one of the 3 allowed concomitant AEDs. However, changes to ketogenic diet (eg, median chain triglyceride level) are not allowed during the study.

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

Use of the following AEDs during the course of the study is not allowed:

- Perampanel
- Vigabatrin
- Cannabinoids
- Benzodiazepines for non-epilepsy indications (eg, anxiety/sleep disorders) (Stable doses of benzodiazepine or intermittent benzodiazepine use as rescue medication for seizure control is allowed)
- Enzyme-inducing antiepileptic drugs (EIAEDs, eg, carbamazepine, oxcarbazepine, eslicarbazepine, phenytoin, phenobarbital, and primidone)

Concomitant use of medications known to be potent CYP3A inducers/inhibitors including, but not limited to, rifampin, troglitazone, St John's Wort, efavirenz, nevirapine, modafinil, pioglitazone, and rifabutin will not be permitted and are to be discontinued within 28 days before Visit 1.

9.4.7.2 Restrictions During the Study Period

Study drug will be administered on the day of each Treatment Visit (ie, Visit 2, Visit 3, Visit 4, and Visit 5) after an overnight fast of at least 8 hours. Treatments will be administered orally 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 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.

For study visits where IPS-EEG assessments will be performed, subjects will be required to abstain from watching television or using any device with an animated screen (ie, computer, video games, tablets, or smart phone) from the time of arrival at the study center until study procedures are completed for that day. 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 before each treatment day. Subjects will be instructed to get similar amounts of sleep prior to each visit.

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/designee 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, and race/ethnicity.

9.5.1.2 Screening 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 the Screening Visit (Visit 1), as specified in the Schedule of Procedures/Assessments (Table 4). This sample will be tested for common drugs of use/abuse: eg, ethyl alcohol, phencyclidine (PCP), benzodiazepines, cocaine, amphetamines, cannabinoids, opioids, barbiturates, and tricyclic antidepressant drugs.

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, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples for the determination of plasma concentrations of E2082 will be collected from each subject. PK sampling for plasma concentration will be collected predose (within 2 hours) and postdose at 1 (±10 min), 2 (±10 min), 4 (±15 min), 6 (±15 min), and 8 (±15 min) hours on each treatment day (ie, Visit 2, Visit 3, Visit 4, and Visit 5). Plasma concentrations of E2082 will be measured using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method. Actual PK sampling date and time will be recorded at each scheduled and unscheduled sampling time point. Actual date and time of study drug administration will also be recorded for each dose administration during each Treatment Visit. See Table 5 for a description of assessment timings and window periods.

At time points when vital signs, ECGs, and blood sampling are to be performed at the same time point, these procedures will be performed in the following order: ECGs, vital signs, and then blood sampling.

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, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

All PD assessments will be performed within ±15 minutes of the scheduled time point. See Table 5 for a description of assessment timings and window periods.

IPS-EEG

Throughout the study, the flash frequency will be recorded. Three eye conditions (eye closure, eyes closed, and eyes open) per stimulus for assessment purposes will be recorded. The combination of lower and upper frequencies gives a total of 3 photosensitivity ranges, 1 per eye condition. If there is any doubt of the interpretation during any of the assessments (for example blinking during the eyes open condition, provoking epileptiform activity) the stimulation in the same eye condition will be repeated. In order to minimize the risk of inducing a seizure, photic stimulation will not be carried out between the upper and lower thresholds. This method has been found to be the safest, as it prevents elicitation of seizures by avoiding stimulation of the subject at the most sensitive frequencies. The range for each subject will be recorded in the CRF. The most sensitive eye condition will be noted during every visit; however, assessments in all 3 eye conditions will be noted.

During the Screening Visit (Visit 1), IPS-EEG assessment will be performed at 5 time points, over a 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. However, the final determination of study eligibility will include predose assessments when the subject returns to study site for Visit 2.

PD activity of E2082 will be assessed by suppression of PPR following IPS under 3 eye conditions (eye closure, eyes closed, and eyes open) using the Grass PS 33 photic stimulator with an unpatterned glass lamp and an intensity of 100 cd/m^2/flash at approximately 30 minutes to 2 hours predose, and at 1, 2, 4, 6, and 8 hours postdose (within ±15 minutes of each scheduled time point), on each treatment day, (ie, Visit 2, Visit 3, Visit 4, and Visit 5). The time course (30 minutes to 2 hours predose to 8 hours postdose) will help assess the onset, maximum change from baseline, and duration of the reduction in PPR response. The predose assessment serves as the baseline on each treatment day. PPR is expected to be within the range of 2 Hz to 60 Hz, depending on the subject's 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 epileptiform activity). 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

In order to enable discrimination between spontaneous and IPS evoked discharges, the subject will be assessed ,at the start of each treatment day, (ie, Visit 2, Visit 3, Visit 4, and Visit 5), for ≥2.5 minutes with each of the 3 eye conditions without any stimulation. Each IPS-EEG assessment will be conducted in all 3 eye conditions (eye closure, eyes closed, and eyes open; each for a minimum of 2.5 minutes) at ascending and then descending photo stimulation frequencies. The lower and upper limit of photosensitivity to IPS threshold frequency will be determined for each eye condition. Trains of flashes at constant frequency will be delivered for 4 to 6 seconds. Intervals between successive flash trains at a given frequency will last for at least 5 seconds. Determination of the photosensitivity ranges will be assessed with separate trains of flashes of 4 to 6 seconds duration (or less if generalized epileptic activity occurs). Flashes will be administered at standard frequencies of 2, 5, 8, 10, 13, 15, 18, 20, 23, 25, 30, 40, 50, and 60 Hz.

Bond and Lader Visual Analogue Scale

The Bond and Lader VAS (Bond A, 1974) for CNS–related effects of E2082 (such as somnolence, sedation, dizziness, and body sway) will be evaluated for each subject predose (within 2 hours) and at 1, 2, 4, 6, and 8 hours postdose on each treatment day (ie, Visit 2, Visit 3, Visit 4, and Visit 5).

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; pregnancy test for women of childbearing potential only; and the performance of neurological and physical examinations as detailed in Table 4.

An assessment of suicidality using the C-SSRS will be performed as detailed in Table 4.

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 E2082.

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 (ie, Follow-up/Early Discontinuation Visit). SAEs must be collected for 28 days after the last dose.

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 QT interval corrected by the Fridericia formula (QTcF) 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, blood chemistry, and urinalysis, are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 4) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. Subjects will fast for at least 8 hours before blood is drawn for clinical laboratory assessments. Clinical laboratory blood collection must be performed before a subject can receive the light snack that can be provided at 30 minutes predose. See Table 5 for a description of assessment timings and window periods.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Blood 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], heart rate [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 4). Vital signs are to be taken in the supine position after subjects have remained resting for at least 5 minutes. All BP measurements should be performed on the same arm, preferably by the same qualified healthcare professional.

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 minimize the potential effects of blood drawing on recordings obtained during safety assessments.

At time points when vital signs, ECGs, and blood sampling are to be performed at the same time point, these procedures will be performed in the following order: ECGs, vital signs, and then blood sampling. Subjects will remain rested in the supine position for 10 minutes before and 5 minutes after ECG recordings, followed by recording of vital sign measurements.

See Table 5 for a description of assessment timings and window periods.

9.5.1.5.5 PHYSICAL EXAMINATIONS

Full and abbreviated physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 4). 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. Clinically significant abnormal findings from the physical examination will be recorded as an AE on the AE CRF.

Full Physical Examination

A full 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

Full and abbreviated neurological examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 4). 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. Clinically significant abnormal findings from the neurological examination will be recorded as an AE on the AE CRF.

9.5.1.5.7 ELECTROCARDIOGRAMS

ECGs (12-lead) will be obtained as designated in the Schedule of Procedures/Assessments (Table 4). At time points when vital signs, ECGs, and blood sampling are to be performed at the same time point, these procedures will be performed in the following order: ECGs, vital signs, and then blood sampling. Subjects will remain rested in the supine position for 10 minutes before and 5 minutes after ECG recordings, followed by recording of vital sign measurements.

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.

See Table 5 for a description of assessment timings and window periods.

9.5.1.5.8 OTHER SAFETY ASSESSMENTS

C-SSRS

An assessment of suicidality using the C-SSRS will be performed at Screening, during each Treatment visit (ie, Visit 2, Visit 3, Visit 4, and Visit 5), and at the Follow-up/Early

discontinuation visit, as designated in the Schedule of Procedures/Assessments (Table 4). It is recommended that, for the Treatment Visits, C-SSRS be performed predose to ensure there is no increased risk of suicidality since last visit.

Pregnancy Test

For women of childbearing potential, a serum β-hCG or hCG test (6 mL blood sample) will be performed during Screening Visit (Table 4). Subsequently, urine pregnancy test will be performed prior to dose administration on each treatment visit (ie, Visit 2, Visit 3, Visit 4, and Visit 5), and upon return to site during Follow-up/Early Discontinuation Visit. Unscheduled pregnancy test (serum or urine) may be performed as medically necessary at the discretion of the investigator.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of procedures/assessments for the study.

Table 4 Schedule of Procedures and Assessments in E2082-A001-201

Phase	Pretreatment	Treatment				Follow-up[a]/Early Discontinuation[b]	Unscheduled Visit
		Randomized Crossover			Open-label		
Period	Screening	Trt Pd 1	Trt Pd 2	Trt Pd 3	Trt Pd 4		
Visit	**1**	**2**	**3**	**4**	**5**	**6[a]**	
Study Day	**-21 to -1**	**1**	**15±3**	**29±3**	**43±3**	**57±3[a]**	
Procedures/Assessments							
Informed Consent	X						
Demography	X						
Randomization		X					
Inclusion/exclusion criteria	X	X					
Medical and surgical history	X						
Epilepsy medical history	X						
Height[c] and weight	X	X				X	(X)[d]
Physical examination[e]	X	X				X	(X)[d]
Neurological examination[f]	X	X	X	X	X	X	(X)[d]
Vital signs[g,h]	X	X	X	X	X	X	(X)[d]
12-Lead ECG[i,h]	X	X	X	X	X	X	(X)[d]
Clinical laboratory tests[j,h]	X	X	X	X	X	X	(X)[d]
Serology (HBsAg, HCV Ab)	X						
Urine drug test[k]	X						

Table 4 Schedule of Procedures and Assessments in E2082-A001-201

Phase	Pretreatment	Treatment				Follow-up[a]/Early Discontinuation[b]	Unscheduled Visit
		Randomized Crossover			Open-label		
Period	Screening	Trt Pd 1	Trt Pd 2	Trt Pd 3	Trt Pd 4		
Visit	**1**	**2**	**3**	**4**	**5**	**6[a]**	
Study Day	**-21 to -1**	**1**	**15±3**	**29±3**	**43±3**	**57±3[a]**	
Procedures/Assessments							
Serum β-hCG [or hCG] test[l]	X						
Urine pregnancy test[l]		X	X	X	X	X	(X)[d]
PK sampling (plasma)[m,h]		X	X	X	X		(X)[d]
IPS-EEG Assessment	X[n]	X[o]	X[o]	X[o]	X[o]		
BL-VAS[p]		X	X	X	X		
C-SSRS[q]	X	X	X	X	X	X	(X)[d]
Study drug administration		X	X	X	X		
Prior and concomitant medication(s)	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

β-hCG = beta-human chorionic gonadotropin (or hCG = human chorionic gonadotropin), BL-VAS = Bond and Lader Visual Analogue Scale, C-SSRS = Columbia-Suicide Severity Rating Scale, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, IPS-EEG = intermittent photic stimulation electroencephalogram, Pd = Period, PK = pharmacokinetics, QTcF = QT interval corrected by the Fridericia formula, Trt = Treatment, VAS = visual analogue scale.

a: For subjects who completed Open-label Treatment Period. Follow-up visit is to be conducted 2 weeks ±3 days following the last day of study product administration.

b: For subjects who discontinued early from the study after having been exposed to study drug, Early Discontinuation Visit is to be conducted 2 weeks ±3 days following the last dose administration. Early Discontinuation visit is not required for subjects who discontinued from the study before receiving the first study drug administration.

Table 4 Schedule of Procedures and Assessments in E2082-A001-201

Phase	Pretreatment	Treatment				Follow-up[a]/Early Discontinuation[b]	Unscheduled Visit
		Randomized Crossover			Open-label		
Period	Screening	Trt Pd 1	Trt Pd 2	Trt Pd 3	Trt Pd 4		
Visit	1	2	3	4	5	6[a]	
Study Day	-21 to -1	1	15±3	29±3	43±3	57±3[a]	
Procedures/Assessments							

c: Height will be assessed only during the Screening Visit.

d: During the unscheduled visits, specific procedure(s) to be performed will be on an as-needed basis at the discretion of the investigator. For example, ECG will only be done if the results from the previous visit were deemed to be clinically significant by the investigator.

e: A full physical examination will be conducted at Screening. Abbreviated physical examination will be performed during Visit 2 (before randomization) and Follow-up/Early Discontinuation Visit. Additional physical examination may be conducted at any other visit(s), as medically deemed necessary. Clinically significant abnormal findings from the physical examinations will be reported as AEs.

f: A full neurological examination will be conducted at Screening. Abbreviated neurological examination will be performed during each treatment visit (predose and at 4 hours [±30 min] postdose) and Follow-up/Early Discontinuation Visit. Clinically significant abnormal findings from the neurological examinations will be reported as AEs.

g: Vital signs (systolic and diastolic blood pressure [BP], heart rate [HR], respiratory rate, and body temperature) will be taken at Screening, during each treatment visit, and during Follow-up/Early Discontinuation Visit. On each treatment day (ie, Visit 2, Visit 3, Visit 4, and Visit 5), vital sign measurements will be obtained predose (within 2 hours), and at 1, 2, 4, 6, and 8 hours postdose, with the window for collection postdose is (±15 min) at each scheduled timepoint. Vital signs are to be taken in the supine position after subjects have remained resting for at least 5 minutes.

h: At time points when vital signs, ECG, and blood sampling are to be performed at the same time point, the following order must be followed: ECG, vital signs, and then blood sampling.

i: ECG assessments will be performed at Screening, during each treatment visit (predose and at 4 hours [±30 min] postdose), and during Follow-up/Early Discontinuation Visit. ECG measurements are to be taken in the supine position after subjects have remained resting for at least 5 minutes. If QTcF exceeds 450 msec during any visit, 3 consecutive ECG measurements each separated by 5 – 10 minutes will be performed to confirm the abnormality. Any ECG abnormalities that the investigator deems to be clinically significant will be reported as AEs.

j: Clinical laboratory tests include: hematology, blood chemistry, and urinalysis. Subjects will fast for at least 8 hours before blood is drawn for clinical laboratory assessments. Clinical laboratory blood collection must be performed before a subject can receive the light snack that can be provided at 30 minutes predose.

Table 4 Schedule of Procedures and Assessments in E2082-A001-201

Phase	Pretreatment	Treatment				Follow-up[a]/Early Discontinuation[b]	Unscheduled Visit
		Randomized Crossover			Open-label		
Period	Screening	Trt Pd 1	Trt Pd 2	Trt Pd 3	Trt Pd 4		
Visit	1	2	3	4	5	6[a]	
Study Day	-21 to -1	1	15±3	29±3	43±3	57±3[a]	
Procedures/Assessments							

k: Screening for common drugs of use/abuse (eg, ethyl alcohol, phencyclidine (PCP), benzodiazepines, cocaine, amphetamines, cannabinoids, opioids, barbiturates, and tricyclic antidepressant drug).

l: For female subjects of childbearing potential only.

m: Blood samples for plasma PK will be obtained predose (within 2 hours) and at 1 (±10 min), 2 (±10 min), 4 (±15 min), 6 (±15 min), and 8 (±15 min) hours postdose on each treatment day (ie, Visit 2, Visit 3, Visit 4 and Visit 5).

n: During Screening Visit, IPS-EEG assessment will be performed at 5 time points over a 4-hour interval (0, 1, 2, 3, and 4 hours; within ±15 minutes of the scheduled time point).

o: On each treatment day (Visit 2, Visit 3, Visit 4, and Visit 5), IPS-EEG assessment will be performed predose (approximately within 30 minutes to 2 hours), and at 1, 2, 4, 6, and 8 hours postdose (a window of ±15 minutes is allowed at each postdose timepoint).

p: BL-VAS will be performed from each subject on each treatment day predose (within 2 hours) and at 1, 2, 4, 6, and 8 hours postdose.

q: C-SSRS will be performed at Screening, during each Treatment Visit (recommended to administer C-SSRS predose to ensure there is no increased risk of suicidality since last visit), and at the Follow-up/Early Discontinuation Visit.

Table 5 presents the blood sampling schedule for pharmacokinetic assessments, in addition for window periods for study assessments on Treatment visits (ie, Visit 2, Visit 3, Visit 4, and Visit 5).

Table 5 Time Windows for Study Assessments on Treatment Days

Visit (Window)	Time Relative to the Administration	Acceptable Time Window
PK		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days)	Predose	–2 hours
	1, 2 hours	±10 minutes
	4, 6, and 8 hours	±15 minutes
Vital Signs		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days)	Predose	–2 hours
	1, 2, 4, 6, and 8 hours	±15 minutes
ECG		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days)	Predose	–2 hours
	4 hours	±30 minutes
Clinical Laboratory Tests		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days)	Predose	–2 hours to -30 minutes (before light snack)
IPS-EEG Assessment		
Visit 2 Visit 3 (±3 days), Visit 4 (±3 days), Visit 5 (±3 days)	Predose	-2 hours to -30 minutes
	1, 2, 4, 6, and 8 hours	±15 minutes

IPS-EEG = intermittent photic stimulation electroencephalogram, PK = pharmacokinetics

9.5.2.2 Description of Procedures/Assessments Schedule

The scheduling of study procedures and assessments is shown in Table 4.

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, CNS-related side effects (eg, somnolence, body sway, dizziness and sedation) known to be associated with AMPA receptor antagonism will also be assessed using BL-VAS (Bond A, 1974). As BL-VAS measures effects of E2082 that are related to the underlying pharmacological activities of AMPA receptor antagonist, these measurements also serve as PD markers in this study.

The IPS-EEG procedure during this study will be performed based upon the protocol of Kastelejin et al (Kasteleijn-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 IPS-EEG 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 (ie, Follow-up/Early Discontinuation visit) and for 28 days after the last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

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

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

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

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 early after having been exposed to study drug are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 4). Early Discontinuation visit is not required for subjects who discontinued from the study before receiving the first study drug administration.

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 during each Treatment Period. A diminution in response is anticipated with the dose range. .

The primary endpoint, the mean change from baseline of the average PPR in the most sensitive is analyzed using a mixed effects model for crossover part of the study and summarized for each E2082 dose level and placebo regardless of crossover design. Another endpoint will include proportions of subjects with complete suppression, partial response, or no response

Complete suppression is defined as an SPR reduction to 0 over at least 1 time point for all 3 eye conditions. Partial response is defined as a reduction in SPR of at least 3 units from baseline for at least 3 time points, and no time points with at least 3 units of increase, in the most sensitive eye condition; without meeting the complete suppression definition. The definition of no response is as follows: Did not meet complete suppression or partial response definitions.

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.

9.7.1.1.2 SECONDARY ENDPOINTS

- Mean change from baseline in the PPR range in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- Onset, maximum change, and duration of response in each of the 3 eye conditions (eye closure, eyes closed, and eyes open)
- Frequency and percentage of subjects with complete suppression, partial response, and no response of SPR
- Changes from baseline in BL-VAS
- Incidence of TEAEs
- Clinically significant changes from baseline in vital signs, serum chemistries, complete blood counts, or liver function tests after single doses of E2082, compared to placebo
- PK parameters of E2082 (C_{max}, t_{max}, area under concentration-time curve from time 0 to 8 hours postdose [$AUC_{(0-8h)}$])

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Relationship between plasma exposure of E2082 (PK) and PD response (eg, onset, maximum change, and duration of photosensitivity response, BL-VAS)

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 PK 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 PD 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 E2082 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, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The Safety Analysis Set will be used for listings of individual E2082 plasma concentrations. The PK analysis set will be used for summaries of plasma E2082 concentrations and for analyses, 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 E2082. These parameters will include, but are not limited to:

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

The PK of E2082 will be analyzed based on available data from this study. The PK and PD Analysis Sets will be used to evaluate the relationship of PK of E2082 and change in SPR response. The PK-PD analyses may include the examination of the relationship of PK of E2082 and SPR (eg, time of onset, maximum change, and duration of response; and BL-VAS data) using model-based approaches, data permitting. Details of the PK/PD analyses will be described in a separately prepared analysis plan and its report.

Analysis variables: Plasma concentrations of E2082

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

Analysis methods: The PK of E2082 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, PHARMACOGENOMIC, AND OTHER BIOMARKER 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 in the most sensitive and 3 eye conditions will be analyzed using a mixed effects model for the crossover part of the study and summarized for each E2082 dose level and placebo regardless of crossover design. The mixed effects model for the crossover part of the study will include treatment (E2082 2.5 mg, 25 mg, and placebo), 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 E2082 dose (2.5 mg or 25 mg) compared to placebo, and 90% CIs will be presented with no adjustments for multiplicity.

Additional analysis by graphical exploration for the evaluation of onset, maximum change, and duration of photosensitivity response at each dose level will be performed for all 3 eye conditions for each treatment. Similarly, frequency and percentage of subjects with complete suppression, partial suppression, and no response at each dose level of E2082 will be summarized descriptively and graphically for each treatment.

Sensitivity analyses may be conducted for photosensitivity response, for example, in subjects who completed all 3 Treatment Periods 1 through 3 versus those who are included in the PD Analysis Set. Other exploratory analyses may be conducted as data permit.

All other PD data (ie, BL-VAS data) 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.

PK-PD analyses may include the examination of the relationship of PK of E2082 and SPR (eg, time of onset, maximum change, and duration of response; and BL-VAS data) using model-based approaches, data permitting. Details of the PK/PD analyses will be described in a separately prepared analysis plan and its report.

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. 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, heart rate, 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 QTcF during the Treatment Period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

- For the QT interval assessment, clinically abnormal ECG results for QT interval corrected for heart rate using 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.

Upon consultation with the sponsor, subjects who discontinue from the study early may be replaced.

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

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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, computed tomography [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 IB, 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 PI (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;

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				seizures
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

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

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2082-A001-201

Study Protocol Title: A Multicenter, Double-Blind, Randomized, Crossover, Single-Dose Study with An Open-Label Treatment Period Evaluating Pharmacodynamic Activity of E2082 in Adult Subjects with Photosensitive Epilepsy

Investigational Product Name: E2082

IND Number: 134556

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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2082-A001-201
Study Protocol Title:	A Multicenter, Double-Blind, Randomized, Crossover, Single-Dose Study with An Open-Label Treatment Period Evaluating Pharmacodynamic Activity of E2082 in Adult Subjects with Photosensitive Epilepsy
Investigational Product Name:	E2082
IND Number:	134556

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