Eslicarbazepine Acetate
Clinical Study Protocol SEP093-701

Efficacy and Safety of Eslicarbazepine Acetate as First Add-on to Levetiracetam or Lamotrigine Monotherapy or as Later Adjunctive Treatment for Subjects with Uncontrolled Partial-onset Seizures: A Multicenter, Open-label, Non-randomized Trial

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician		
Medical Monitor		
SAE/Pregnancy Reporting		

1. SYNOPSIS

Name of Sponsor: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: Aptiom®

Name of Active Ingredient: Eslicarbazepine acetate (ESL)

Title of Study: Efficacy and Safety of Eslicarbazepine Acetate as First Add-on to Levetiracetam or Lamotrigine Monotherapy or as Later Adjunctive Treatment for Subjects with Uncontrolled Partial-onset Seizures: A Multicenter, Open-label, Non-randomized Trial

Proposed Indication: Adjunctive treatment for subjects with partial-onset seizures (POS)

Study Centers: Multicenter with sites in the United States and Canada

Phase of Development: 4

Study Objectives:

Primary Objective: To evaluate the effectiveness (measured by study retention rate) of ESL administered once daily (QD) as the first adjunctive therapy to levetiracetam (LEV) or lamotrigine (LTG) or as later adjunctive therapy in subjects with POS over a 24-week maintenance period in a real-world clinical setting.

Secondary Objectives:

- To evaluate the efficacy of ESL QD as a first or later adjunctive therapy based on the number of seizures reported via a standardized paper daily diary over a 24-week maintenance period.
- To evaluate the safety and tolerability of ESL QD as a first or later adjunctive therapy.
- To evaluate the effect of treatment with ESL QD on the quality of life (QOL), behavior, and mood.

Exploratory Objectives:

- To evaluate the accuracy of an investigational wearable watch device from Empatica in recording seizure counts.
- To evaluate the performance of an investigational electronic seizure diary in the form of a smartphone application (Empatica MATE).

Study Design:

This is a 31-week, multicenter, 2-arm, prospective, open-label, non-randomized, Phase 4 study of ESL as adjunctive therapy in adult subjects with a diagnosis of epilepsy with POS. Two groups of ESL-naïve subjects will be evaluated. The groups are defined as follows:

- Arm 1 (ESL as first add-on): This group will include subjects who have been maintained on a regimen consisting of a stable dose of LEV or LTG for at least 1 month (28 days) prior to screening and who have not used any adjunctive treatment.
- Arm 2 (ESL as later add-on): This group will include subjects who have been maintained on a regimen consisting of a stable dose of 1 - 2 anti-epileptic drugs (AEDs) (excluding oxcarbazepine [OXC]) for at least 1 month (28 days) prior to screening and who have used adjunctive treatment in the past.

The Arm 1 subjects will allow an assessment of the efficacy and safety of ESL in subjects who are early in the course of their disease and being treated with one of the most common first line AEDs. The subjects in Arm 2 are similar to the subject population in the Phase 3 adjunctive studies, treatment-resistant subjects who are later in the course of their disease. The inclusion of these subjects in the present study will provide an assessment of the efficacy and safety of ESL as a later adjunctive therapy in a real world clinical setting. In addition, this study will provide data from both Arm 1 and Arm 2 for several behavioral, mood-related, and QOL-related assessments that were not evaluated in in the Phase 3 program.

Approximately 190 subjects will be enrolled (approximately 93 subjects in Arm 1 and 97 subjects in Arm 2).

The study will consist of a Screening Phase of 1 to 2 weeks, followed by a 2-week Titration Phase, a 24-week Maintenance Phase, and a Safety Follow-up/Taper Phase of 4 weeks. The last visit in the Maintenance Phase (Visit 9) is considered the End of Study (EOS) visit.

The screening visit should take place 7 - 10 days prior to the titration visit, and may be extended to 7 - 17 days if required with consent of medical monitor. Subjects of Asian ancestry who require HLA-B*1502 testing (eg do not have prior test results) may have the screening visit 7 - 17 days prior to the titration visit.

Subjects who withdraw prior to the EOS visit should have an Early Discontinuation Visit (EDV) within 72 hours.

During the study, there will be 9 site visits and 2 scheduled telephone visits. The follow-up contact to collect information on AEs and concomitant medications may occur at a site visit or by a telephone call.

The procedures and assessments performed in this study are described in Table 2.

The study population has been selected to be similar to subjects treated in a clinical setting. The study will include subjects ≥ 18 years old who meet the study inclusion, do not meet exclusion criteria and who can provide written informed consent. In order to be eligible for participation in the study, subjects of Asian ancestry (or subjects for whom the absence of Asian ancestry cannot be confirmed) must sign an additional genetic consent to undergo blood testing for the human leukocyte antigen (HLA)-B*1502 allele unless they can provide documentation of prior testing to confirm non-carrier status. Asian ancestry will be based on subject self-report.

Signed informed consent, (including genetic consent for subjects of Asian ancestry, or subjects for whom the absence of Asian ancestry cannot be confirmed) will be obtained prior to performing any study procedures.

Subjects will complete the pre-Human Epilepsy Project (HEP) instrument at screening. The HEP instrument is a form administered by an Investigator to obtain a retrospective seizure history, in as accurate a manner as possible, in the absence of a retrospective seizure diary. The caregiver may contribute to the HEP data. These data will be used for seizure history only. As part of completing the HEP instrument, the Diagnostic Interview for Seizure Classification Outside of Video EEG Recording (DISCOVER) will be administered. The DISCOVER form allows researchers to ask subjects with epilepsy questions about the subject's seizures in order to increase the likelihood of proper diagnosis and to standardize seizure classification. The intent is to ensure that the subject will use correct and consistent terminology to describe seizure history and when they complete their daily seizure diaries throughout the study. The information on the seizures recorded on the DISCOVER form will not be utilized for seizure analyses; it will be used for diagnostic and coding purposes only.

Seizure history at screening will be derived from the HEP. The subject will be asked about the number and types of seizures that occurred for the longest available period up to 3 months prior to screening. These data will be recorded by the Investigator on a separate seizure history case report form.

During the study, the number of seizures by type will be obtained from subject entries in a standard

paper seizure diary and electronic seizure diary daily starting at Visit 1 and up to Visit 9 (EOS, the end of the 24-week Maintenance Phase). The diaries require an entry every day whether a seizure occurs or not. Subjects will record information for each seizure by date and type of seizure.

The subject will also be issued an investigational wearable seizure detection device at Visit 1 to collect exploratory data evaluating the identification of seizure activity based on skin conduction. The subject will wear the watch throughout the duration of the study, up to Visit 9.

Eligible subjects will begin the 2-week Titration Phase on Day 1 (Week 1), during which they will initiate treatment with ESL 400 mg/day and remain on that dose for 1 week (Days 1 – 7). Subjects will titrate to ESL 800 mg/day the beginning of week 2 (Day 8) and will remain on that dose for 1 week up to the beginning of the maintenance phase. Subjects will maintain a minimum dose of 800 mg/day for the Maintenance Phase; however, during the Maintenance Phase, subjects may titrate in weekly increments of 400 mg/day as medically indicated at the discretion of the Investigator up to a maximum dose of 1200 mg/day (Canadian sites) or 1600 mg/day (United States [US] sites), (based on maximum local labelled dose). Additional details are provided in Section 10.1.1.

Subjects who complete the 24-week Maintenance Phase may choose to continue treatment with commercial ESL. Subjects who chose not to continue treatment with ESL at the end of the Maintenance Phase will be gradually tapered off drug provided that they do not have an AE that requires abrupt discontinuation of the study drug.

Subjects who prematurely discontinue treatment with ESL for any reason will be gradually tapered off study drug unless abrupt discontinuation of the drug is required for the treatment of an AE. Subjects who prematurely discontinue treatment with ESL will be withdrawn from the study.

Subjects should maintain their concomitant AED(s) at a constant dosage during the Titration Phase and Maintenance Phase of the study. However, subjects on concomitant carbamazepine (CBZ) may have a dose reduction (up to 25% of the total daily dose taken at study entry) in the last week of the titration period (Week 2) or the first week of the Maintenance Phase (Week 3), if the subject has intolerable AEs related to an association between CBZ and ESL in the opinion of the Investigator. This reduction must be approved by the Medical Monitor. In addition, subjects taking phenytoin who experience intolerable AEs suggestive of phenytoin toxicity may have their dose of phenytoin reduced up to 15%, with the approval of the Medical Monitor. For patients who become seizure free during the trial, patients may reduce dose of baseline AEDs by a maximum of 25% to improve overall tolerability at the discretion of the Investigator. After the end of the Maintenance Phase, AEDs may be adjusted at the discretion of the Investigator.

Subjects who are tolerant of ESL who have not had a rash or allergic reaction for at least 6 weeks and who provide a separate optional written genetic consent will be asked for a saliva sample for HLA genotyping. They will also be asked to complete a questionnaire relating to rash risk factors at or after Visit 4. Information from subjects who participate will be used as the control group in a separate rash registry study of risk associated with HLA type.

Subjects who report a serious adverse event (SAE) of rash or other allergic reaction regardless of causality at any time during the study will be asked to provide consent to be contacted by the University of Pennsylvania on behalf of Sunovion for participation in the separate rash registry study.

Number of Subjects (planned): Approximately 190 subjects will be enrolled as available to either Arm 1 or Arm 2 as defined above.

Diagnosis and Main Criteria for Subject Inclusion:

Following are the main inclusion and exclusion criteria, complete lists of all inclusion and exclusion criteria for this study are provided in Section 8.

Main Inclusion Criteria

- Male or female subjects ≥ 18 years of age.

- Subject is willing and able to sign informed consent.
- Subject has a documented diagnosis of epilepsy with simple POS with a motor component or complex POS with or without secondarily generalized seizures as defined in the Classification of Seizures of the International League Against Epilepsy (ILAE, 1981).
- Subject has a documented electroencephalogram within 10 years prior to screening.
- Subject has had at least 3 POS during previous six months.
- Subject has had a sufficient number of seizures at time of enrollment to justify adjunctive therapy, as determined by the Investigator.
- Subjects are required to be ESL-naïve *AND*
  - Maintained on a stable LEV or LTG regimen for at least 1 month (28 days) prior to screening with no history of adjunctive treatment (for Arm 1, ESL as first add-on).

  OR
  - Maintained on a stable dose of 1 - 2 AEDs (excluding OXC) for at least 1 month (28 days) prior to screening and who have had prior adjunctive treatment (for Arm 2, ESL as later add-on).
- Except for epilepsy, subject is judged to be in general good health based on medical history, physical examination findings, and clinical laboratory test results.

Main Exclusion Criteria

- Subjects with a prior exposure to ESL.
- Subjects currently being treated with OXC.
- Subject with a history of allergic reaction to OXC or CBZ, or a history of serious allergic reaction (Stevens-Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms or similar) to any AED, or a history of serious allergic reactions to other medications.
- Subject has a history of status epilepticus or cluster seizures (ie, 3 or more seizures within 30 minutes) within the 3 months prior to screening.
- Subject has had seizures of psychogenic origin or purely subjective seizures within the last 2 years.
- Subject has a known progressive structural central nervous system (CNS) lesion, progressive encephalopathy, or a progressive cerebral abnormality.
- Subject whose current seizures are related to an acute medical illness or other non-epileptic origin.
- Subjects who are not able to complete the diaries in the Investigator's opinion.
- Subject is pregnant, currently nursing, or intends to become pregnant during the study period or within 30 days of the last dose of study drug.
- Subjects of Asian ancestry will be excluded if they are carriers of HLA-B*1502. Either:
  - Subject must give written informed consent for genotyping, and test negative.

  OR
  - Subjects must provide documentation of prior testing confirming non-carrier status.

Study Drug (Aptiom), Dosage and Mode of Administration:

The drug dosage form will be commercial tablets of 400 mg Aptiom (ESL) in 30 count bottles with an added supplemental study label. An Interactive Web/Voice Response System will be used to manage subject screening and enrollment.

Tablets will be taken by mouth, QD.

Aptiom may be taken with or without food. Tablets may be crushed and mixed with food if the subject is incapable of swallowing a tablet. All tablets must be taken simultaneously. Subjects are to take study drug at approximately the same time each day.

Duration of Treatment: 30 weeks

Reference Therapy, Dosage and Mode of Administration: None

Concomitant Medications:

The following medications are prohibited during the study. Subject may not have taken any medication prohibited for this protocol within 4 weeks prior to screening.

- OXC.
- Warfarin, felbamate, vigabatrin, and perampanel (unless at stable dose with safety testing for ≥1 year).
- Ezogabine.
- Other experimental/investigational drugs taken as part of a clinical trial.

The following drugs and treatments are allowed during the study:

- Vagus nerve stimulation.
- Steroids.
- Benzodiazepines at stable dose (as AEDs).
- Chronic medications (other than those prohibited, taken at a stable dose).
- Any other drug that, in the opinion of the Investigator is necessary for the medical treatment of the subject, provided it is not a prohibited medication.

See Section 10.2 to Section 10.4 of the full protocol for further discussion of concomitant medications.

Study Endpoints:

Primary Endpoint: The proportion of subjects completing 24 weeks adjunctive therapy during Maintenance Phase (Visit 9).

Efficacy Endpoints:

- Seizure data via the paper diary will be used to calculate the following seizure related endpoints:
  - Standard Seizure Frequency (SSF) during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
  - 50% and 75% responder rate (calculated as 50% and 75% reduction in SSF from baseline) as evaluated during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
  - Relative reduction (%) in SSF from baseline during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
  - Proportion of seizure-free subjects during the first 12 weeks, the last 12 weeks, and the

24 weeks of the Maintenance Phase.

- Time on ESL.

Other Endpoints:

- Changes from baseline in the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)-6-item questionnaire.
- Changes from baseline in the Profile of Mood States Short-form (POMS-SF).
- Changes from baseline in the agitation/behavioral measurements as evaluated by the Modified Overt Aggression Scale (MOAS).
- Changes from baseline in Quality of Life in Epilepsy-Patient-Weighted (QOLIE-31-P) scores.
- Changes from baseline in EuroQol Five Dimensions Questionnaire (EQ-5D) scores.
- Clinical Global Impression of Improvement (CGI-I) scores at each evaluation time point.
- Patient's Global Impression of Change (PGI-C) scores at each evaluation time point.

Safety Endpoints:

- Number and percentage of subjects with AEs.
- Number and percentage of subjects with SAEs.
- Number and percentage of subjects with AEs leading to discontinuation.
- Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS): Proportion (%) of events in each classification class (as completed by the subject).
- Changes from baseline in clinical laboratory parameters including thyroid panel.
- Changes from baseline in vital signs parameters.
- Score of AED-specific AEs (by the Liverpool Adverse Event Profile [LAEP]).

Exploratory Endpoints:

- Seizure data recorded by an investigational wearable watch device from Empatica.
- Seizure data recorded by an investigational electronic seizure diary from Empatica MATE application.

Statistical Methods: The Statistical Analysis Plan will provide details on the statistical methods planned for this study and will be finalized prior to the database lock. All endpoints will be summarized descriptively for Arm 1 and Arm 2 separately. There will be no statistical comparisons between Arm 1 and Arm 2.

The proportion of subjects completing 24 weeks of the Maintenance Phase and the 95% confidence interval (CI) will be calculated. SSF, 50% and 75% responder rates, relative reduction in SSF, and proportion of seizure-free subjects during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase will be calculated separately. Time on ESL will be calculated from the first dose to the last known dose of ESL.

All AEs will be summarized by calculating the number and percent of subjects with AEs, system organ class and preferred term. Deaths, serious AEs, and AEs leading to study discontinuation will be summarized.

Clinical laboratory and vital signs variables will be summarized by calculating summary statistics on the actual values and on the change from baseline. Shift tables from baseline to the end of this study

will be provided for laboratory parameters.

For eC-SSRS score, the percentage of subjects in each classification class for overall and at each assessment time will be summarized.

NDDI-E, POMS-SF, MOAS, QOLIE-31-P, and EQ-5D scores will be summarized for each evaluation time point; changes from baseline will also be summarized. CGI-I and PGI-C scores will be summarized for each evaluation time point.

Sample Size:

Arm 1 (first add-on): Assuming a completion rate of 60% at 24 weeks of the Maintenance Phase for Arm 1, to show the lower limit of the 95% CI in the rate to be 50% (50%, 70%), the sample size is estimated at approximately 93 subjects.

Arm 2 (later add-on): Assuming the completion rate of 50% at 24 weeks of the Maintenance Phase for Arm 2, to show the lower limit of the 95% CI in the rate to be 40% (40%, 60%), the sample size is estimated at approximately 97 subjects.

Total estimates subjects enrollment is approximately 190 subjects.

Sample size is calculated based on the precision (a half width of the 95% CI) for the estimate of the completion rate as assumed as above and is used the Normal approximation to the Binomial distribution.

Table 2: Schedule of Assessments

Study Period	Screening	Titration[a]	24-Week Maintenance Phase[a]									EDV[a]	Safety Follow-up
Visit	V1	V2	V3	V4	TC1	V5	V6	TC2	V7	V8	V9 (EOS)		V10 or TC3
Week	-1 to -2[o] WKs	WK 1 Day 1	WK 3	WK 7	WK 9	WK 11	WK 15	WK 17	WK 19	WK 23	WK 27	-	WK 31
Windows (days)	(+3)[o]	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	±7
Procedures													
Informed Consent Form	X	-	-	-	-	-	-	-	-	-	-	-	-
Genetic Consent for HLA-B*1502 Characterization: Subjects of Asian Ancestry only[b,o]	X	-	-	-	-	-	-	-	-	-	-	-	-
Genetic Consent for HLA genotyping (optional)[c]	X	-	-	-	-	-	-	-	-	-	-	-	-
Review of Inclusion/ Exclusion Criteria	X	X	-	-	-	-	-	-	-	-		-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-
Medical and Neurologic History	X	-	-	-	-	-	-	-	-	-	-	-	-
Complete DISCOVER form	X	-	-	-	-	-	-	-	-	-	-	-	-
Administer HEP and Collect Seizure History Data[d]	X	-	-	-	-	-	-	-	-	-	-	-	-
Prior/Concomitant Medications[e]	X	X	X	X	-	X	X	-	X	X	X	X	X
Physical/Neurologic Examination	X	-	X	X	-	X	X	-	-	X	X	X	-
Vital Signs	X	X	X	X	-	X	X	-	X	X	X	X	-
Body Weight	X	X	X	X	-	X	X	-	X	X	X	X	-
Height	X	-	-	-	-	-	-	-	-	-	-	-	-

Table 2: Schedule of Assessments (Continued)

Study Period	Screening	Titration[a]	24-Week Maintenance Phase[a]									EDV[a]	Safety Follow-up
Visit	V1	V2	V3	V4	TC1	V5	V6	TC2	V7	V8	V9 (EOS)		V10 or TC3
Week	-1 to -2[o] WKs	WK 1 Day 1	WK 3	WK 7	WK 9	WK 11	WK 15	WK 17	WK 19	WK 23	WK 27	-	WK 31
Windows (days)	+3 [o]	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	±7
Procedures													
12-lead ECG	X	-	-	-	-	-	-	-	-	-	X	X	-
Clinical Laboratory Tests[f]	X	-	-	-	-	-	-	-	-	-	X	X	-
Thyroid panel (free T3, T4, and TSH)	X	-	-	-	-	-	-	-	-	-	X	X	-
Blood Sample for HLA-B*1502 testing: Subjects of Asian ancestry only[g]	X	-	-	-	-	-	-	-	-	-	-	-	-
Genetic Saliva Sample and Questionnaire (optional)[h]	-	-	-	X	-	-	-	-	-	-	-	-	-
Serum β-hCG[i]	X	-	-	-	-	-	-	-	-	-	X	X	-
Urine Pregnancy Test[i]	-	X	X	X	-	X	X	-	X	X			
Urine Drug Screen	X												
Liverpool Adverse Event Profile[j]	-	X	X	X	-	X	X	-	X	X	X	X	-
Adverse Events	-	X	X	X	X	X	X	X	X	X	X	X	X
Pre-treatment Adverse Events	X	-	-	-	-	-	-	-	-	-	-	-	-
Dispense Study Drug	-	X	X	X	-	X	X	-	X	X	X[k]	X[p]	-
Collect Study Drug	-	-	X	X	-	X	X	-	X	X	X	X	-

Table 2: Schedule of Assessments (Continued)

Study Period	Screening	Titration[a]	24-Week Maintenance Phase[a]									EDV[a]	Safety Follow-up
Visit	V1	V2	V3	V4	TC1	V5	V6	TC2	V7	V8	V9 (EOS)		V10 or TC3
Week	-1 to -2[o] WKs	WK 1 Day 1	WK 3	WK 7	WK 9	WK 11	WK 15	WK 17	WK 19	WK 23	WK 27	-	WK 31
Windows (days)	+3 [o]	-	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	±7
Procedures													
Record Any ESL Dose Change Since Last Visit	-	-	X	X	X	X	X	X	X	X	X	-	-
Record Any AED Dose Change Since Last Visit	-	-	X	X	X	X	X	X	X	X	X	X	-
Distribute Empatica Watch[l]	X	-	-	-	-	-	-	-	-	-	-	-	-
Distribute Electronic Seizure Diary[m]	X	-	-	-	-	-	-	-	-	-	-	-	-
Distribute Paper Seizure Diary[m]	X	X	X	X	-	X	X	-	X	X	X	X	-
Collect Paper Seizure Diary	-	X	X	X	-	X	X	-	X	X	X	X	-
Review Seizure Diaries		X	X	X	-	X	X	-	X	X	X	X	X[q]
EQ-5D	-	X	-	-	-	X	-	-	-	-	X	X	-
CGI-I	-		X	-	-	X	-	-	-	-	X	X	-
PGI-C	-		X	-	-	X	-	-	-	-	X	X	-
QOLIE-31-P	-	X	-	-	-	X	-	-	-	-	X	X	-
POMS-SF	-	X	-	-	-	X	-	-	-	-	X	X	-
NDDI-E	-	X	-	-	-	X	-	-	-	-	X	X	-
MOAS	-	X	-	-	-	X	-	-	-	-	X	X	-
eC-SSRS[n]	X	X	X	X	-	X	X	-	X	X	X	X	-
Return of watch and data collection device	-	-	-	-	-	-	-	-	-	-	X	X	-

Abbreviations: AED = Antiepileptic drug; β-hCG = Beta-human chorionic gonadotropin; CGI-I – Clinical Global Impression of Improvement; CRF = case report form; eC-SSRS = electronic Columbia-Suicide Severity Rating Scale; DISCOVER = Diagnostic Interview for Seizure Classification Outside of Video EEG Recording; ECG = Electrocardiogram; EDV = Early Discontinuation Visit; EOS = End of Study; EQ-5D = EuroQol Five Dimensions Questionnaire; ESL = Eslicarbazepine acetate; HEP = pre-Human Epilepsy Project; HLA = Human Leukocyte Antigen; MOAS = Modified Overt Aggression Scale; NDDI-E = Neurological Disorders Depression Inventory for Epilepsy; PGI-C = Patient's Global Impression of Change; POMS-SF = Profile of Mood States Short-form; QOLIE-31-P = Quality of Life in Epilepsy-Patient-Weighted (31-item); T3 = Triiodothyronine; T4 = Thyroxine; TC = telephone call; TSH = Thyroid Stimulating Hormone; US = United States; WK = Week

[a] Eligible subjects will begin the 2-week Titration Phase on Day 1 (Week 1), during which they will initiate treatment with ESL at 400 mg/day and remain on that dose for 1 week (Days 1 – 7). Subjects will titrate to ESL 800 mg/day the beginning of week 2 (Day 8) and will remain on that dose for 1 week up to the beginning of the maintenance phase. Subjects will maintain a minimum dose of 800 mg/day for the Maintenance Phase; however, during the Maintenance Phase, subjects may titrate in weekly increments of 400 mg/day as medically indicated at the discretion of the Investigator up to a maximum dose of 1200 mg/day (Canadian Sites) or 1600 mg/day (US sites), (based on maximum local labelled dose). Additional details are provided in Section 10.1.1. Subjects who withdraw prior to the (end of study) EOS visit should have an early discontinuation visit (EDV) within 72 hours.

[b] Subjects of Asian ancestry (or subjects for whom the absence of Asian ancestry cannot be confirmed) who cannot provide documentation stating that they are not carriers of HLA-B*1502 must give written informed consent for genotyping. Asian ancestry will be based on subject self-report.

[c] This consent for genetic saliva sample and associated questionnaire is optional.

[d] Record seizure history (the number and types of seizures that occurred over the longest available period up to 3 months prior to screening).

[e] Record all prior and concomitant medications, including over the counter medications, taken within the previous 60 days.

[f] Includes clinical chemistry, hematology and urinalysis. Estimated creatinine clearance using Cockcroft-Gault equation at Screening only.

[g] Required for subjects of Asian ancestry (or subjects for whom the absence of Asian ancestry cannot be confirmed) and who do not have documentation to show that they are not carriers of HLA-B*1502.

[h] Subjects who provided optional separate informed consent/assent only.

[i] A serum pregnancy test will be given to all female subjects of childbearing potential at screening. An on-site urine pregnancy test will be given to all female subjects of childbearing potential at Visits 1-8. Any positive urine pregnancy test will be followed up with a serum test for confirmation of pregnancy. A serum pregnancy test will be given to all females subjects of childbearing potential at Visit 9 (EOS) or at the EDV.

[j] The Liverpool Adverse Event Profile collects information on AEs associated with AEDs.

[k] Subjects who elect to continue on commercially available drug will not be dispensed additional ESL at this visit. Subjects who elect to discontinue ESL will be provided sufficient ESL to accommodate the appropriate taper regimen.

[l] Subjects will be provided with the Empatica watch and instructed in the use of the watch.

[m] Subjects will be provided a standardized paper daily seizure diary and an electronic daily seizure diary and instructed in the use of the diaries. Diaries are to be completed daily whether a seizure occurs or not.

[n] The "Baseline/Screening" (lifetime) version should be administered at the screening visit and the "Since Last Visit" version at all other time points.

[o] The screening visit should take place 7 - 10 days prior to the titration visit, and may be extended to 7 – 17 days if required with consent of medical monitor. Subjects of Asian ancestry who require HLA-B*1502 testing (eg, do not have prior test results) may have the screening visit 7 - 17 days prior to the titration visit.

[p] Subjects who discontinue prior to the EOS visit will be provided sufficient ESL to accommodate the appropriate taper regimen.

[q] At the Safety Follow-Up visit, the standardized paper daily seizure diary will not be collected; however it will be reviewed as part of the subject's safety assessments.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are shown in Table 3 and Table 4.

Table 3: List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
AED	Anti-epileptic drugs
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
β-hCG	Beta-human chorionic gonadotropin
CBZ	Carbamazepine
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CI	Confidence Interval
CNS	Central nervous system
CRF	Case report form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DISCOVER	Diagnostic Interview for Seizure Classification Outside of Video EEG Recording (form)
ECG	Electrocardiogram
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
EDV	Early discontinuation visit
EOS	End of study
EQ-5D	EuroQol Five Dimensions Questionnaire
ESL	Eslicarbazepine acetate
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HEP	Pre-Human Epilepsy Project instrument
HLA	Human leukocyte antigen
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
ILAE	International League Against Epilepsy

Table 3: List of Abbreviations (Continued)

Abbreviation	Full Form
IPD	Important protocol deviations
IRB	Institutional Review Board
IXRS	Interactive Web/Voice Response System
LAEP	Liverpool Adverse Event Profile
LEV	Levetiracetam
LTG	Lamotrigine
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
MOAS	Modified Overt Aggression Scale
NDDI-E	Neurological Disorders Depression Inventory for Epilepsy
OXC	Oxcarbazepine
PGI-C	Patient's Global Impression of Change
POS	Partial-onset seizures
POMS-SF	Profile of Mood States Short-form
PPD-PVG	PPD Pharmacovigilance
PT	Preferred term
QD	Once daily
QOL	Quality of life
QOLIE-31-P	Quality of Life in Epilepsy-Patient-Weighted (31-item)
SAE	Serious adverse event
SOC	System organ class
SSF	Standard seizure frequency
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid stimulating hormone
VNS	Vagal nerve stimulation
WBC	White blood cell
WHO-DRUG	World Health Organization drug dictionary

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Screened Subject	Any subject who signed the study specific informed consent and completed at least one study-related procedure.
Screen Failures	Any subject who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening, but was not enrolled.
Study Drug	Term used for study drug provided by the Sponsor (ESL, ie, Aptiom).
Treatment Period	The period of the study in which the study drug is administered.
Enrolled Subject	Any subject who was successfully screened and enrolled into the titration period of the study.
Completed Subject	Any subject who completed all the Schedule of Assessments up to and including assessments for the end of the Maintenance Phase (Visit 9, the end of the study).
Early Termination Subject	Any subject who was successfully screened and entered the treatment period of the study, but did not complete the study.
End of Study	The day that the subject completes the study per the study design (end of the Maintenance Phase, Visit 9).

4. INTRODUCTION

4.1. Epilepsy

Epilepsy, defined by the recurrence of spontaneous unprovoked seizures (ie, not caused by systemic, metabolic or toxic disorders) affects more than 50 million adults and children worldwide (CPMP, 2009). Globally, an estimated 2.4 million people are diagnosed with epilepsy each year. In high-income countries, annual new cases are between 30 and 50 per 100,000 people in the general population. In low-and middle-income countries, this figure can be up to two times higher (World Health Organization). There are no known geographic or racial differences in the occurrence of the disease; it occurs in both men and women and can begin at any age, but is more frequent in infancy, childhood, adolescence, and old age.

The primary marker of the disease is recurrent seizures which are classified in the International Classification of Epileptic Seizures as generalized, partial or focal, and unclassified (Dreifuss, 1981). Partial seizures, which are related to a focal brain dysfunction, are the most frequent type (approximately 60% of cases).

Anti-epileptic drugs (AEDs) are the major therapeutic intervention for subjects with epilepsy and approximately 60% of newly diagnosed patients are seizure free on a single AED. However, about 40% of subjects are not satisfactorily controlled and many patients suffer from significant adverse events (AEs) (CPMP, 2009). This lack of seizure control leads to combination therapy, but significant proportions of subjects continue to have regular seizures despite therapy with more than one AED. This suggested the need for a more selective and less toxic AED, which led to the development of eslicarbazepine acetate (ESL).

4.2. Study Conduct Rationale

ESL is approved for the treatment of partial-onset seizures (POS) as monotherapy or adjunctive therapy in adults in the US. ESL is approved in Canada as adjunctive therapy in the treatment of POS in patients with epilepsy who are not satisfactorily controlled with conventional therapy. The current open-label study is designed to investigate the use of ESL in a real-life clinical setting in both subjects early in the course of their disease (those using ESL as a first add-on) and in a treatment-resistant population (similar to those evaluated in the Phase 3 adjunctive studies). The treatment-resistant subjects are included in this study to assess effectiveness of ESL as a later adjunctive therapy in a clinical setting in order to determine if the data from Phase 3 studies are representative of real world treatment. In addition, there will be several additional behavioral, mood-related, and quality of life (QOL)-related assessments in this study that were not evaluated in the Phase 3 program. Therefore, this study will provide new information about the effect of adjunctive treatment with ESL in subjects early in the course of their disease and in treatment-resistant subjects.

This study will be performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulatory requirements.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective is to evaluate the effectiveness (measured by study retention rate) of ESL administered once daily (QD) as the first adjunctive therapy to levetiracetam (LEV) or lamotrigine (LTG) or as later adjunctive therapy in subjects with POS over a 24-week maintenance period in a real-world clinical setting.

5.2. Secondary Objectives

- To evaluate the efficacy of ESL QD as a first or later adjunctive therapy based on the number of seizures reported via a standardized paper daily diary over a 24-week maintenance period.
- To evaluate the safety and tolerability of ESL QD as a first or later adjunctive therapy.
- To evaluate the effect of treatment with ESL QD on the QOL, behavior, and mood.

5.3. Exploratory Objectives

- To evaluate the accuracy of an investigational wearable watch device from Empatica in recording seizure counts.
- To evaluate the performance of an investigational electronic seizure diary in the form of a smartphone application (Empatica MATE).

6. STUDY ENDPOINTS

6.1. Primary Endpoint

The primary endpoint is the proportion of subjects completing 24 weeks adjunctive therapy during Maintenance Phase (Visit 9).

6.2. Efficacy Endpoints

- Seizure data via the paper diary will be used to calculate the following seizure related endpoints:
  - Standard Seizure Frequency (SSF) during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
  - 50% and 75% responder rate (calculated as 50% and 75% reduction in SSF from baseline) as evaluated during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
  - Relative reduction (%) in SSF from baseline during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
  - Proportion of seizure-free subjects during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.
- Time on ESL.

6.3. Other Endpoints

- Changes from baseline in the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)-6-item questionnaire.
- Changes from baseline in the Profile of Mood States Short-form (POMS-SF).
- Changes from baseline in the agitation/behavioral measurements as evaluated by the Modified Overt Aggression Scale (MOAS).
- Changes from baseline in Quality of Life in Epilepsy-Patient-Weighted (QOLIE-31-P) scores.
- Change from baseline in EuroQol Five Dimensions Questionnaire (EQ-5D) scores.
- Clinical Global Impression of Improvement (CGI-I) scores at each evaluation time point.
- Patient's Global Impression of Change (PGI-C) scores at each evaluation time point.

6.4. Safety Endpoints

- Number and percentage of subjects with AEs.
- Number and percentage of subjects with serious adverse events (SAEs).

- Number and percentage of subjects with AEs leading to discontinuation.
- Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS): Proportion (%) of events in each classification class (as completed by the subject).
- Changes from baseline in clinical laboratory parameters, including thyroid panel.
- Changes from baseline in vital signs parameters.
- Score of AED-specific AEs (by the Liverpool Adverse Event Profile [LAEP]).

6.5. Exploratory Endpoints

- Seizure data recorded by an investigational wearable watch device from Empatica.
- Seizure data recorded by an investigational electronic seizure diary from Empatica MATE application.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a 31-week, multicenter, 2-arm, prospective, open-label, non-randomized, Phase 4 study of ESL as adjunctive therapy in adult subjects with a diagnosis of epilepsy with POS. Two groups of ESL-naïve subjects will be evaluated. The groups are defined as follows:

- Arm 1 (ESL as first add-on): This group will include subjects who have been maintained on a regimen consisting of a stable dose of LEV or LTG for at least 1 month (28 days) prior to screening and who have not used any adjunctive treatment.
- Arm 2 (ESL as later add-on): This group will include subjects who have been maintained on a regimen consisting of a stable dose of 1-2 AEDs (excluding oxcarbazepine [OXC]) for at least 1 month (28 days) prior to screening and who have used adjunctive treatment in the past.

The Arm 1 subjects will allow an assessment of the efficacy and safety of ESL in subjects who are early in the course of their disease and being treated with one of the most common first line AEDs. The subjects in Arm 2 are similar to the subject population in the Phase 3 adjunctive studies, treatment-resistant subjects who are later in the course of their disease. The inclusion of these subjects in the present study will provide an assessment of the efficacy and safety of ESL as a later adjunctive therapy in a real world clinical setting. In addition, this study will provide data from both Arm 1 and Arm 2 for several behavioral, mood-related, and QOL-related assessments that were not evaluated in the Phase 3 program.

Approximately 190 subjects will be enrolled (approximately 93 subjects in Arm 1 and 97 subjects in Arm 2).

The study will consist of a Screening Phase of 1 to 2 weeks, followed by a 2-week Titration Phase, a 24-week Maintenance Phase, and a Safety Follow-up/Taper Phase of 4 weeks. The last visit in the Maintenance Phase (Visit 9) is considered the End of Study (EOS) visit.

The screening visit should take place 7 - 10 days prior to the titration visit, and may be extended to 7 – 17 days if required with consent of medical monitor. Subjects of Asian ancestry who require HLA-B*1502 testing (eg, do not have prior test results) may have the screening visit 7 - 17 days prior to the titration visit.

Subjects who withdraw prior to the EOS visit should have an Early Discontinuation Visit (EDV) within 72 hours.

During the study, there will be 9 site visits and 2 scheduled telephone visits. The follow-up contact to collect information on AEs and concomitant medications may occur at a site visit or by a telephone call.

The procedures and assessments performed in this study are described in Table 2.

The study population has been selected to be similar to subjects treated in a clinical setting. The study will include subjects ≥ 18 years old who meet the study inclusion, do not meet exclusion criteria and who can provide written informed consent. In order to be eligible for participation in the study, subjects of Asian ancestry (or subjects for whom the absence of Asian ancestry cannot

be confirmed) must sign an additional genetic consent to undergo blood testing for the human leukocyte antigen (HLA)-B*1502 allele unless they can provide documentation of prior testing to confirm non-carrier status. Asian ancestry will be based on subject self-report. A full description of inclusion/exclusion criteria is available in Section 8.

Signed informed consent (including genetic consent for subjects of Asian ancestry, or subjects for whom the absence of Asian ancestry cannot be confirmed) will be obtained prior to performing any study procedures.

Subjects will complete the pre-Human Epilepsy Project (HEP) instrument at screening. The HEP instrument is a form administered by an Investigator to obtain a retrospective seizure history, in as accurate a manner as possible, in the absence of a retrospective seizure diary. The caregiver may contribute to the HEP data. These data will be used for seizure history only. As part of completing the HEP instrument, the Diagnostic Interview for Seizure Classification Outside of Video EEG Recording (DISCOVER) will be administered. The DISCOVER form allows researchers to ask subjects with epilepsy questions about the subject's seizures in order to increase the likelihood of proper diagnosis and to standardize seizure classification. The intent is to ensure that the subject will use correct and consistent terminology to describe seizure history and when they complete their daily seizure diaries throughout the study. The information on the seizures recorded on the DISCOVER form will not be utilized for seizure analyses; it will be used for diagnostic and coding purposes only. Additional information on the DISCOVER form and the HEP instrument are available in Section 11.2.2.1 and Section 11.2.2.2, respectively.

Seizure history at screening will be derived from the HEP. The subject will be asked about the number and types of seizures that occurred for the longest available period up to 3 months prior to screening. These data will be recorded by the Investigator on a separate seizure history case report form.

During the study, the number of seizures by type will be obtained from subject entries in a standard paper diary and an electronic seizure diary daily starting at Visit 1 and up to Visit 9 (EOS, the end of the 24-week Maintenance Phase). The diaries require an entry every day whether a seizure occurs or not. Subjects will record information for each seizure by date and type of seizure. A full description of the use of the seizure diaries is provided in Section 11.2.2.4.

The subject will also be issued an investigational wearable seizure detection device at Visit 1 to collect exploratory data evaluating the identification of seizure activity based on skin conduction. The subject will wear the watch throughout the duration of the study, up to Visit 9. Additional details are available in Section 11.2.3.

Eligible subjects will begin the 2-week Titration Phase on Day 1 (Week 1), during which they will initiate treatment with ESL 400 mg/day and remain on that dose for 1 week (Days 1 - 7). Subjects will titrate to ESL 800 mg/day the beginning of week 2 (Day 8) and will remain on that dose for 1 week up to the beginning of the maintenance phase. Subjects will maintain a minimum dose of 800 mg/day for the Maintenance Phase; however, during the Maintenance Phase, subjects may titrate in weekly increments of 400 mg/day as medically indicated at the discretion of the Investigator up to a maximum dose of 1200 mg/day (Canadian sites) or 1600 mg/day (US sites) (based on maximum local labelled dose). Additional details are provided in Section 10.1.1.

Subjects who complete the 24-week Maintenance Phase may choose to continue treatment with commercial ESL. Subjects who chose not to continue treatment with ESL at the end of the Maintenance Phase will be gradually tapered off drug provided that they do not have an AE that requires abrupt discontinuation of the study drug.

Subjects who prematurely discontinue treatment with ESL for any reason will be gradually tapered off study drug. However, abrupt discontinuation of the drug is permitted for the treatment of an AE. Subjects who prematurely discontinue treatment with ESL will be withdrawn from the study.

Subjects should maintain their concomitant AED(s) at a constant dosage during the Titration Phase and Maintenance Phase of the study. However, subjects on concomitant carbamazepine (CBZ) may have a dose reduction (up to 25% of the total daily dose taken at study entry) in the last week of the Titration Phase (Week 2) or the first week of the Maintenance Phase (Week 3), if the subject has intolerable AEs related to an association between CBZ and ESL in the opinion of the Investigator. This reduction must be approved by the Medical Monitor. In addition, subjects taking phenytoin who experience intolerable AEs suggestive of phenytoin toxicity may have their dose of phenytoin reduced up to 15%, with the approval of the Medical Monitor. For patients who become seizure free during the trial, patients may reduce dose of baseline AEDs by a maximum of 25% to improve overall tolerability at the discretion of the Investigator. After the end of the Maintenance Phase, AEDs may be adjusted at the discretion of the Investigator.

Subjects who are tolerant of ESL who have not had a rash or allergic reaction for at least 6 weeks and who provide a separate optional written genetic consent will be asked for a saliva sample for HLA genotyping. They will also be asked to complete a questionnaire relating to rash risk factors at or after Visit 4. Information from subjects who participate will be used as the control group in a separate rash registry study of risk associated with HLA type.

Subjects who report a SAE of rash or other allergic reaction regardless of causality at any time during the study will be asked to provide consent to be contacted by the University of Pennsylvania on behalf of Sunovion for participation in the separate rash registry study.

Details of the study assessments and other procedures to be performed at each visit are presented in Table 2, Schedule of Assessments, and Section 11, Study Assessments. If necessary, subjects may return to the clinic at any time for an unscheduled visit.

7.2. Treatment Assignment and Blinding

This is an open-label, and non-randomized study. Subjects will be assigned to 1 of 2 treatment arms defined by their prior treatment with AEDs as described for Arm 1 and Arm 2 above in Section 7.1.

7.3. Rationale

7.3.1. Rationale for the Study Design

This study is designed to evaluate the long-term effectiveness, safety, and tolerability, (as measured by study retention over the 24-week Maintenance Phase) of ESL given as adjunctive therapy in adult subjects ≥ 18 years of age. The study will assess effectiveness and safety of ESL when administered as adjunctive therapy in ESL-naïve subjects who have never used adjunctive

therapy previously and in ESL-naïve subjects who have used adjunctive therapy previously, but are seeking additional therapeutic options. The open-label design is appropriate to assess safety and tolerability in this subject population.

7.3.2. Rationale for the Dosages

The ESL doses for this study have been selected based on approved adult ESL doses in the US (1600 mg QD) and Canada (1200 mg QD).

7.3.3. Rationale for the Study Population

This study is designed to investigate the use of ESL in a real-life clinical setting. In order to evaluate ESL in the type of patients encountered in clinical practice, it includes both subjects early in the course of their disease and in treatment-resistant subjects later in the course of their disease who have tried adjunctive therapy in the past.

7.3.4. Rationale for the Endpoints

The primary endpoint, retention in the study throughout the 24-week Maintenance Phase, was selected because both efficacy and tolerability/safety factor into the subject's willingness to complete this phase of the study. Therefore, retention is a good measure of the effectiveness of ESL in clinical practice.

Standard measurements are used for the evaluation of changes in seizure activity, safety and evaluations of quality of life, mood and behavior.

8. SELECTION OF SUBJECTS

8.1. Subject Inclusion Criteria

The subjects who fulfill the following criteria will be included in the study.

1. Male or female subjects ≥ 18 years of age.
2. Subject is willing and able to sign informed consent.
3. Subject has a documented diagnosis of epilepsy with simple POS with a motor component or complex POS with or without secondarily generalized seizures as defined in the Classification of Seizures of the International League Against Epilepsy (ILAE, 1981).
4. Subject has a documented electroencephalogram within 10 years prior to screening.
5. Subject has had at least 3 POS during previous six months.
6. Subject has had a sufficient number of seizures at time of enrollment to justify adjunctive therapy, as determined by the Investigator.
7. Subjects are required to be ESL-naïve AND
   a. Maintained on a stable LEV or LTG regimen for at least 1 month (28 days) prior to screening with no history of adjunctive treatment (for Arm 1, ESL as first add-on).

      OR

   b. Maintained on a stable dose of 1-2 AEDs (excluding OXC) for at least 1 month (28 days) prior to screening and who have had prior adjunctive treatment (for Arm 2, ESL as later add-on).
8. If the subject is treated with any stimulation device for epilepsy (Vagal Nerve Stimulation [VNS], Responsive Neurostimulator [RNS], or similar), the device must have been implanted at least 6 months before screening and the device parameters must be documented as stable for at least 1 month prior to screening. (Note: these devices will not be counted as concomitant AED).
9. Except for epilepsy, subject is judged to be in general good health based on medical history, physical examination findings, and clinical laboratory test results.

8.2. Subject Exclusion Criteria

1. Subjects with a prior exposure to ESL.
2. Subjects currently being treated with OXC.
3. Subject with a history of allergic reaction to OXC or CBZ, or a history of serious allergic reaction (Stevens-Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms or similar) to any AED, or a history of serious allergic reactions to other medications.

4. Subjects who have taken warfarin, felbamate, vigabatrin, or perampanel, (unless at stable dose with safety testing for ≥ 1 year) within a 4-week period prior to screening.
5. Subjects taking ezogabine.
6. Subject has taken any medication prohibited for this protocol within 4 weeks prior to Screening (see Section 10.4).
7. Subjects using benzodiazepines on more than an occasional basis (defined as more than 2 times per week), except when used chronically as an AED (see exclusion criteria 26).
8. Seizure disorder characterized primarily by simple POS without motor signs.
9. Subject has a history of primarily generalized seizures (eg, myoclonic, absence, tonic).
10. Subject has a history of status epilepticus or cluster seizures (ie, 3 or more seizures within 30 minutes) within the 3 months prior to screening.
11. Subject has had seizures of psychogenic origin or purely subjective seizures within the last 2 years.
12. Subject has had seizures too close to count accurately.
13. Subject has a known progressive structural central nervous system (CNS) lesion, progressive encephalopathy, or a progressive cerebral abnormality.
14. Subject whose current seizures are related to an acute medical illness or other non-epileptic origin.
15. Subjects of Asian ancestry will be excluded if they are carriers of HLA-B*1502. Either:
    a. Subject must give written informed consent for genotyping, and test negative.

    OR

    b. Subjects must provide documentation of prior testing confirming non-carrier status.
16. Subject has a major medical illness other than epilepsy that would prevent safe participation in this study, at the discretion of the Investigator, including (but not limited to) cardiac disease, thyroid disease, hepatic or renal impairment, endocrine or metabolic disease, gastrointestinal disease, or hematologic disease. Note: Active medical conditions that are minor or well-controlled are not exclusionary if they do not affect risk to the subject or the study results. If the effect of the condition in regard to the risk to the subject or to the study results is unclear, the Medical Monitor should be consulted.
17. Subjects with clinically relevant laboratory abnormalities at screening (eg, sodium < 130 mEq/L, alanine transaminase (ALT) or aspartate transaminase (AST) > 2.0 times the upper limit of the normal, white blood cell [WBC] count < 3,000 cells/mm^3, estimated creatinine clearance < 50 mL/min, or has values for thyroid testing (free triiodothyronine (T3), free thyroxine (T4), thyroid stimulating hormone [TSH]) indicating the presence of significant thyroid dysfunction.
18. Subject has a history or presence of abnormal electrocardiogram (ECG), which in the Investigator's opinion is clinically significant or QT interval corrected for heart rate using the Fridericia method (QTcF) of ≥ 450 msec per screening ECG.

19. Subject has second- or third-degree atrioventricular block that is not corrected with a pacemaker.
20. Subjects who meet the Diagnostic and Statistical Manual of Mental Disorders, 5th edition text revision defined criteria for major depressive episode within the last 6 months. Subjects with mild, chronic depression without recent hospitalization who are being maintained on a stable dose of a single antidepressant are acceptable.
21. Subject has an active suicidal plan or intent (in the Investigator's opinion) in the past 4 weeks prior to screening.
22. Subject has a history of suicide attempt in the last 2 years prior to screening.
23. Subject has other major psychiatric disorders.
24. Subjects who are not able to complete the diaries in the Investigator's opinion.
25. Subject has a history of alcohol or substance abuse within 2 years prior to screening for study participation, or subjects currently using alcohol, drugs of abuse, or any prescribed or over-the-counter medication in a manner, which, in the opinion of the Investigator, indicates abuse.
26. Subject tests positive for drugs of abuse at screening. Note: Subjects with a positive drug screen for marijuana, amphetamines, opiates, or benzodiazepines, who have a documented prescription for a medical condition and are on a stable dose of this prescribed medication for at least 4 weeks prior to screening, may be eligible to participate in the study upon approval from the Medical Monitor.
27. Subject is pregnant, currently nursing, or intends to become pregnant during the study period or within 30 days of the last dose of study drug.
28. Subject has participated in any investigational study within 30 days prior to screening, as documented in subject's medical history.
29. Subject is a clinical or investigational site staff member or relative of a staff member.
30. Any other condition or circumstance that, in the opinion of the Investigator, may compromise the subject's ability to comply with the study protocol.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Description of Study Drug

Drug will be supplied as commercially available Aptiom, 400 mg tablets, 30 count bottle with an added supplemental study label.

9.2. Study Drug Storage

ESL acetate should be stored at the site at United States Pharmacopeia (USP) Controlled Room Temperature (CRT): 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F). Subjects should store ESL at room temperature. ESL should be kept out of reach and sight of children.

9.3. IXRS and Dispensing of Study Drug

An Interactive Web/Voice Response System (IXRS) will be used to register the Screening Visit (Visit 1) and assignment of the Subject Screening number. If the Subject is enrolled in the study the Screening number becomes the Subject number. The IXRS will also be utilized to register the Titration Visit (Visit 2), Maintenance Phase Visits (Visit 3 – Visit 9) and EDV. Study drug will be dispensed based on assignment by the IXRS at Visits 2 – Visit 8. At Visit 9 and EDV the IXRS will give an option to dispense an additional bottle of study drug if needed for taper. Please ensure to dispense the correct lot number(s) assigned to each Subject. In addition the IXRS will be utilized to register Screen Failure and Acknowledgment of study drug receipt at site.

Specific User Manuals will be supplied.

9.4. Study Drug Accountability

The Investigator or designee will maintain accountability records, including the availability of study drug received, study drug dispensation and returns per Sponsor/contract research organization (CRO) instructions.

The date of the first dose of study drug and the amount, the date of last dose of study drug and the amount, and the date of any change of study drug dose and the amount with the reason for the dose change for each alteration will be collected in the database.

The Investigator or designee will collect and document the status of all used and unused study drug from study subjects at appropriate study visits per Sponsor/CRO instructions.

10. TREATMENT OF SUBJECTS

10.1. Study Drug

The drug dosage form will be commercial tablets of 400 mg Aptiom (ESL) in 30 count bottles with an added supplemental study label.

Tablets will be taken by mouth, QD.

Aptiom may be taken with or without food. Tablets may be crushed and mixed with food if the subject is incapable of swallowing a tablet. All tablets must be taken simultaneously. Subjects are to take study drug at approximately the same time each day.

10.1.1. Treatment with Study Drug

Eligible subjects will begin the 2-week Titration Phase on Day 1 (Week 1), during which they will initiate treatment with ESL 400 mg/day and remain on that dose for 1 week (Days 1 - 7). Subjects will titrate to ESL 800 mg/day the beginning of week 2 (Day 8) and will remain on that dose for 1 week up to the beginning of the maintenance phase. Subjects will maintain a minimum dose of 800 mg/day for the Maintenance Phase; however, during the Maintenance Phase, subjects may titrate in weekly increments of 400 mg/day as medically indicated at the discretion of the Investigator up to a maximum dose of 1200 mg/day (Canadian sites) or 1600 mg/day (US sites) (based on maximum local labelled dose).

During the 24-week Maintenance Phase, only one reduction to a minimum of 800 mg/day is permitted. Subjects requiring doses < 800 mg/day will be discontinued from the study.

Subjects who complete the 24-week Maintenance Phase may choose to continue treatment with commercial ESL. Subjects who chose not to continue treatment with ESL for any reason will be gradually tapered off drug unless abrupt discontinuation of the drug is required in response to an AE. The taper schedule is provided in Table 5.

Table 5: Taper of Study Drug

Dose (mg/day)	First Week	Second Week	Third Week
800	400	Stop	Stop
1200	800	400	Stop
1600	800	400	Stop

10.1.2. Premature Discontinuation of Treatment with Study Drug

Subjects who prematurely discontinue treatment with ESL prior to Visit 9 (EOS) for any reason will be gradually tapered off study drug (see Table 5). However, abrupt discontinuation of the drug is permitted for the treatment of an AE. Subjects who prematurely discontinue treatment with ESL (abruptly, or by taper) will be withdrawn from the study.

10.2. Concomitant Antiepileptic Drugs

Subjects should continue treatment with their previously prescribed drugs; background concomitant AEDs will not be supplied by Sunovion. Subjects should maintain their concomitant AED(s) at a constant dosage during the Titration Phase and Maintenance Phase of the study.

However, subjects on concomitant CBZ may have a dose reduction (up to 25% of the total daily dose taken at study entry) in the last week of the titration period (Week 2) or the first week of the Maintenance Phase (Week 3), if the subject has intolerable AEs related to association between CBZ and the study drug in the opinion of the Investigator. This reduction must be approved by the Medical Monitor. In addition, subjects taking phenytoin who experience intolerable AEs suggestive of phenytoin toxicity may have their dose of phenytoin reduced up to 15%, with the approval of the Medical Monitor. For patients who become seizure free during the trial, patients may reduce dose of baseline AEDs by a maximum of 25% to improve overall tolerability at the discretion of the Investigator. After the end of the Maintenance Phase, AEDs may be adjusted at the discretion of the Investigator.

10.3. Prior and Concomitant Medications and Therapies

The following information on all medication administered from screening through End of Study or at Early Termination will be recorded on the case report form (CRF): Medication name, dose, frequency, route, start date, stop date, and indication.

Information on the format and version of coding dictionary is provided in the Data Management Plan. All medications will be coded using the World Health Organization drug dictionary (WHO-DRUG).

10.4. Prohibited Medications

The following medications are prohibited during the study. Subjects may not have taken any medication prohibited for this protocol within 4 weeks prior to screening.

- OXC.
- Warfarin, felbamate, vigabatrin, and perampanel (unless at stable dose with safety testing for ≥ 1 year).
- Ezogabine.
- Other experimental/investigational drugs taken as part of a clinical trial.

10.4.1. Permitted Medications

The following drugs and treatments are allowed

- Vagus nerve stimulation.
- Steroids.
- Benzodiazepines at stable dose (as AEDs).
- Chronic medications, other than those prohibited, taken at a stable dose.

- Any other drug that, in the opinion of the Investigator is necessary for the medical treatment of the subject, provided it is not a prohibited medication.

10.5. Guidance for Overdose

Guidance for overdose is available in the local labelling for Aptiom.

11. STUDY ASSESSMENTS

A summary of assessments to be conducted at each visit is presented in Table 2.

11.1. Medical History, Demographics, and Baseline Characteristics

Demographic and baseline characteristics include date of birth, sex, ethnicity, race, weight, height, brief physical examination results, and medical history will be collected. For medical history, only relevant/significant medical history and recurrence of any condition will be collected. The collection of seizure history is discussed in Section 11.2.2.

11.2. Primary and Efficacy Assessments

11.2.1. Retention Rate

The primary assessment will be retention rate, calculated as the proportion of subjects completing the 24-week Maintenance Phase (Visit 9).

11.2.2. Seizures

11.2.2.1. Seizure Classification

At Screening, the Investigator will administer the Diagnostic Interview for Seizure Classification Outside of Video EEG Recording (DISCOVER) Form. This questionnaire is designed to allow researchers to ask subjects with epilepsy questions about the patient's seizures in order to increase the likelihood of proper diagnosis and to standardize seizure classification. The intent is to ensure that the subject will use correct and consistent terminology to describe the seizures they are experiencing when they report their seizure history and complete their seizure diaries. The information on the seizures recorded on the DISCOVER form will not be utilized for seizure analyses; it will be used for diagnostic and coding purposes only.

11.2.2.2. Pre-Human Epilepsy Project Instrument

At screening, subjects will complete the HEP. The caregiver may contribute to the HEP data. The HEP instrument is a form administered by an Investigator to obtain a retrospective seizure history, in as accurate a manner as possible, in the absence of a retrospective seizure diary. These data will be used for seizure history only.

11.2.2.3. Seizure History

Seizure history at screening will be derived from the HEP. The subject will be asked about the number and types of seizures that occurred for the longest available period up to 3 months prior to screening. These data will be recorded by the Investigator on a separate seizure history case report form.

11.2.2.4. Seizure Diaries

To record seizures during the study, a standardized paper seizure diary and an electronic seizure diary will be dispensed at Visit 1. The subjects will be trained on use of the diaries by the site

personnel. The subjects will also receive a copy of the description of seizure types as presented in the DISCOVER form to ensure that the subject will use correct and consistent terminology to describe the seizures they are experiencing during the study.

The diaries will be completed daily throughout the study, up until the end of the Maintenance Phase (Visit 9, EOS). The diaries require an entry on every day whether a seizure occurs or not. Subjects will record information for each seizure in the paper diary and electronic diary at the same time by date and type of seizure. At each return study visit, the seizure diaries will be reviewed by site staff.

Efficacy evaluations of seizures during the study will be based on the information recorded in the standardized paper daily seizure diary.

11.2.3. Empatica Watch

This study will use the Embrace watch produced by Empatica. Embrace measures physiological data (3-axis accelerometer and gyro, skin conductance, skin temperature), runs pattern analysis, and issues alerts. The watch is designed such that subjects are not aware what data are collected/measured while they are wearing the watch.

The subject should wear the watch on the same arm throughout the study. The watch should be worn on the same side of the body as the subject's seizure focus (side of brain), if known.

For additional details, refer to the study manual.

11.3. Safety Assessments

The Investigator or appropriate designee will review results of safety assessments on a regular basis and the Sponsor must be kept fully informed of any clinically significant findings either at screening or subsequently during study conduct. Safety assessments will be performed at the visits and times outlined in the Schedule of Assessments (Table 2).

11.3.1. Adverse Events

Pretreatment events will be monitored from the time informed consent form (ICF) is provided up until the first ESL dose administration.

Adverse events will be collected for each subject. Adverse events will be collected at study visits and during telephone contact. Subjects should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Section 12.1.1.

AEs will be monitored from the time of first ESL dose administration.

Serious adverse events will be monitored from the time informed consent/assent is obtained.

11.3.2. Clinical Laboratory Tests

11.3.2.1. Safety Laboratory Tests

The clinical laboratory tests required by protocol are listed in Section 20 – Appendix I.

Blood and urine samples will be collected for clinical laboratory tests. All clinical laboratory tests will be performed centrally. For detailed instructions regarding clinical laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Samples will be processed at a central laboratory to ensure consistency. All clinical laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified. Any POC (point of care) kits that are performed on site by study personnel rather than in a lab must be CLIA waived and the study center must possess a CLIA certificate of Waiver.

11.3.2.2. Urine Drug Screen

The urine drug screen will be performed at screening. Urine will be collected at the clinical site in a clean container according to standard procedures.

11.3.2.3. Pregnancy Testing

Serum and urine pregnancy testing will be performed for female subjects as described in the Schedule of Assessments (Table 2).

11.3.3. Genetic Testing

11.3.3.1. Genetic Testing for the HLA-B*1502 Allele

The HLA-B*1502 allele in individuals of Asian ancestry has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome when treated with CBZ. Because this study may include Asian subjects who may be taking CBZ, genetic testing will be conducted at screening in all subjects of Asian ancestry (or subjects for whom the absence of Asian ancestry cannot be confirmed). Genetic testing in these subjects is not required if prior documentation of a negative HLA-B*1502 allele test is available.

11.3.3.2. Genetic Sampling

Subjects who are tolerant to ESL for at least 6 weeks and who provide a separate optional written genetic consent will be asked to provide a saliva sample and provide additional medical history information. Participation is optional. Information from subjects who participate will be used as the control group in a separate rash registry study of risk associated with HLA type. Information will be de-identified and kept confidential.

Subjects who report a SAE of rash or other allergic reaction regardless of causality at any time during the study will be asked to provide consent to be contacted by the University of Pennsylvania on behalf of Sunovion for participation in the separate rash registry study.

11.3.4. Vital Signs

Supine systolic and diastolic blood pressures, respiratory rate, pulse rate, and oral temperature will be measured following 5 minutes of seated rest.

Blood pressure and pulse rate should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and pulse rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of blood pressure and pulse rate throughout the study. If a subject develops symptoms consistent with orthostatic hypotension

(light-headedness, dizziness, or changes in sensorium upon standing) at any point, his or her supine and standing blood pressure and pulse rate should be collected at that time in the manner described above. Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG.

11.3.5. Electrocardiograms

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 10 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples. All attempts should be made to use the same ECG recorder for all visits within individual subjects.

Refer to Section 21 – Appendix II for additional information.

11.3.6. Physical and Neurologic Examinations

A brief physical examination, assessing the subject's overall health and physical condition, will be performed according to the site's standard operating procedures. A brief neurological examination will also be conducted. These examinations will occur at screening and at the time points indicated in Table 2.

11.3.7. Safety Scales

11.3.7.1. Electronic Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation). The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a computer-automated, subject-reported version of the C-SSRS, in which the subject's response to a question prompts and shows the appropriate follow-up questions (if any).

The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior. The eC-SSRS scale takes approximately 5 minutes to administer. Occurrence of suicidal ideation is defined as having answered "yes" to at least one of the 5 suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) at any evaluation. Occurrence of suicidal behavior is defined as having answered "yes" to at least one of the 4 suicidal behavior sub-categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post-baseline evaluation.

The "Baseline/Screening" (lifetime) version should be administered at the screening visit and the "Since Last Visit" version at all other time points.

Subjects who express suicidal ideation or behavior in completion of the eC-SSRS during the course of the study should be evaluated by the investigator and referred to a mental health professional at the discretion of the investigator.

11.3.7.2. The Liverpool Adverse Event Profile

The LAEP is designed as a patient self-report scale to assess the frequency of AED side effects. It includes 19 items rated on a 4-point Likert scale with 1, never a problem; 2, rarely a problem; 3, sometimes a problem; and 4, always a problem. Total scores range from 19 to 76, with high scores indicating more-frequent symptom reporting.

The LAEP is introduced to the participants in the questionnaire with the heading "Here are a few questions about your health generally." The recommended preamble to the scale followed with the words, "During the last 4 weeks, have you had any of the problems listed." The problems include unsteadiness, tiredness, restlessness, feelings of anger or aggression to others, nervousness and/or agitation, headache, hair loss, problems with skin (eg, acne, rash), double or blurred vision, upset stomach, difficulty in concentrating, trouble with mouth or gums, shaky hands, weight gain, dizziness, sleepiness, depression, memory problems, and disturbed sleep.

No indication is given within the questionnaire that the symptoms listed might be linked to the use of medication.

11.4. Clinical Assessments, Quality of Life, Behavior and Mood Scales

11.4.1. EuroQol Five Dimensions Questionnaire

The EQ-5D is made up of 2 components; health state description and overall health evaluation.

In the description part, health status is measured in terms of five dimensions (5D); mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Mobility dimension asks about the person's walking ability. Self-care dimension asks about the ability to wash or dress by oneself, and usual activities dimension measures performance in "work, study, housework, family or leisure activities." In pain/discomfort dimension, it asks how much pain or discomfort they have, and in anxiety/depression dimension, it asks how anxious or depressed they are. The respondents self-rate their level of severity for each dimension using a 5-level scale.

In addition, the respondents evaluate their overall health status using the visual analogue scale.

11.4.2. Clinical Global Impression – Improvement

The CGI-I scale is a 7-point scale that requires an approved rater to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

11.4.3. Patient Global Impression of Change

The PGI-C is a 7-point scale that requires the subject to assess the change (if any) in activity limitations, symptoms, emotions and overall quality of life since treatment. The subject responses include 1) no change (or condition has gotten worse), 2) almost the same, hardly any change at all, 3) a little better, but no noticeable change, 4) somewhat better, but the change has not made any real difference, 5) moderately better, and a slight but noticeable change, 6) better, and a definite improvement that has made a real and worthwhile difference or 7) a great deal better, and a considerable improvement that has made all the difference.

11.4.4. Quality of Life in Epilepsy-Patient-Weighted

The QOLIE-31-P contains seven multi-item scales that investigate the following health concepts: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects and overall QOL. The QOLIE-31-P overall score is obtained using a weighted average of the multi-item scale scores.

11.4.5. POMS-Short Form

The POMS-SF is an instrument designed to assess transient, distinct mood states and consists of a list of 37 adjectives. Respondents indicate the degree to which each adjective describes themselves during the last week using a 5-point Likert scale. This format yields both an overall Total Mood Disturbance score as well as scores for each of the six subscales contained in the original POMS: Fatigue-Inertia, Vigor-Activity, Tension-Anxiety, Depression-Dejection, Anger-Hostility, and Confusion-Bewilderment. The items included in the short form scales are: Depression = unhappy, sad, blue, hopeless, discouraged, miserable, helpless, worthless; Vigor = lively, active, energetic, cheerful, full of pep, vigorous; Confusion = confused, unable to concentrate, bewildered, forgetful, uncertain about things; Tension = Tense, on edge, uneasy, restless, nervous, anxious; Anger = angry, peeved, grouchy (written as grovely in some versions), annoyed, resentful, bitter, furious; Fatigue = worn-out, fatigued, exhausted, weary, bushed.

11.4.6. Neurological Disorders Depression Inventory for Epilepsy

The NDDI-E is a 6-item questionnaire validated to screen for depression in people with epilepsy.

The NDDI-E consists of the following items:

- Everything is a struggle.
- Nothing I do is right.
- Feel guilty.
- I’d be better off dead.
- Frustrated.
- Difficulty finding pleasure.

Each item is rated on a 4-point Likert scale with higher scores indicating a more severe response.

11.4.7. The Modified Overt Aggression Scale

The MOAS is a 4-part behavior rating scale designed to measure four types of aggressive behavior as witnessed in the past week. The MOAS will be completed by an approved rater. Each section consists of 5 questions, with the first section regarding verbal aggression, the second section focusing on aggression against property, the third section measuring autoaggression, and the fourth section concerning physical aggression. Respondents are asked to check whether each statement describes behavior over the previous week.

Total scores on the MOAS range from 0-40, with a higher score indicating more aggressive behavior. Each checked statement receives 1 point, then points from each section are summed.

Section scores are weighted as follows:

Scores from the "Aggression Against Property" section multiplied by 2; Scores from the "autoaggression" section multiplied by 3; Scores from the "physical aggression" section multiplied by 4. Weighted scores are then added together to yield the total score.

11.5. Study Visits and Assessments

11.5.1. Screening: Visit 1 (-1 to -2 Week [+ 3 days])

Subjects will be evaluated at the Screening Visit over the 1- to 2-week Screening Phase to determine their eligibility to enroll in the study. The screening visit should take place 7 – 10 days prior to the titration visit, and may be extended to 7 – 17 days if required with consent of medical monitor. Subjects of Asian ancestry who require HLA-B*1502 testing (eg, do not have prior test results) may have the screening visit 7 - 17 days prior to the titration visit.

Subjects are assigned screening numbers sequentially utilizing the IXRS system.

The following study-related procedures will be performed at screening:

- Obtain signed informed consent for study participation prior to performing any study procedures.
- Obtain signed genetic consent for genotyping in subjects of Asian ancestry (or subjects for whom the absence of Asian ancestry cannot be confirmed) from the subject before conducting any other visit procedures. Note: This consent is not required for subjects who can provide documentation of prior testing to confirm non-carrier status.
- Obtain genetic consent for optional saliva HLA testing.
- Review inclusion/exclusion criteria.
- Record demographics.
- Record medical/neurologic history.
- Complete DISCOVER form.
- Administer HEP Instrument and collect data.
- Record seizure history (the number and types of seizures that occurred for the longest available period up to 3 months prior to screening).
- Record previous medication and concomitant medications including over the counter medications taken within the previous 2 months.
- Perform physical and neurological examination.
- Obtain vital signs, body weight, and height.
- Perform a 12-lead ECG.
- Obtain blood and urine samples for clinical laboratory evaluation (serum chemistry, hematology, urinalysis, and thyroid panel).
- Obtain urine for urine drug screen (UDS).

- Obtain blood sample for HLA-B*1502 testing (subjects of Asian ancestry only, or subjects for whom the absence of Asian ancestry cannot be confirmed). Note: Not required for subjects who can provide documentation of prior testing to confirm non-carrier status.
- For females of childbearing potential, obtain blood for serum beta-human chorionic gonadotropin (β-hCG).
- Record pre-treatment AEs.
- Distribute seizure diaries and instruct the subject in the use of the diaries.
- Distribute Empatica watch and instruct the subject on the use of the watch.
- Administer the eC-SSRS questionnaire.

11.5.2. Titration Phase: Visit 2 (Week 1, Day 1)

- Review of inclusion/exclusion criteria.
- Record concomitant medications.
- Obtain vital signs and body weight.
- For females of childbearing potential, obtain sample for urine pregnancy test (to be confirmed with serum pregnancy test if positive).
- Record LAEP.
- Record AEs.
- Dispense study drug.
- Collect paper seizure diary.
- Distribute paper seizure diary.
- Review seizure diaries.
- Administer questionnaires (EQ-5D, QOLIE-31, POMS-SF, NDDI-E, MOAS, and eC-SSRS).

11.5.3. Start of Maintenance: Visit 3 (Week 3 ± 3 days)

- Record concomitant medications.
- Perform physical and neurological examination.
- Obtain vital signs and body weight.
- For females of childbearing potential, obtain sample for urine pregnancy test (to be confirmed with serum pregnancy test if positive).
- Record LAEP.
- Record AEs.
- Dispense study drug.

- Collect study drug.
- Record any ESL dose change since the last study visit.
- Record any AED dose change since the last study visit.
- Collect paper seizure diary.
- Distribute paper seizure diary.
- Review seizure diaries.
- Administer the questionnaires (CGI-I, PGI-C, and eC-SSRS).

11.5.4. Visit 4 (Week 7 ± 3 days)

- Record concomitant medications.
- Perform physical and neurological examination.
- Obtain vital signs and body weight.
- Collect a saliva sample for characterization of HLA and Questionnaire (optional, for subjects who have signed optional genetic consent and who have been tolerant of ESL without rash or allergic reaction for at least 6 weeks).
- For females of childbearing potential, obtain sample for urine pregnancy test (to be confirmed with serum pregnancy test if positive).
- Record LAEP.
- Record AEs.
- Dispense study drug.
- Collect study drug.
- Record any ESL dose change since the last study visit.
- Record any AED dose change since the last study visit.
- Collect paper seizure diary.
- Distribute paper seizure diary.
- Review seizure diaries.
- Administer the eC-SSRS questionnaire.

11.5.5. Telephone Call 1 (Week 9 ± 3 days)

- Record AEs.
- Record any ESL dose change since the last study visit.
- Record any AED dose change since the last study visit.

11.5.6. Visit 5 (Week 11 ± 3 days)

- Record concomitant medications.
- Perform physical and neurological examination.
- Obtain vital signs and body weight.
- For females of childbearing potential, obtain sample for urine pregnancy test (to be confirmed with serum pregnancy test if positive).
- Record LAEP.
- Record AEs.
- Dispense study drug.
- Collect study drug.
- Record any ESL dose change since the last study visit.
- Record any AED dose change since the last study visit.
- Collect paper seizure diary.
- Distribute paper seizure diary.
- Review seizure diaries.
- Administer questionnaires (EQ-5D, CGI-I, PGI-C, QOLIE-31, POMS-SF, NDDI-E, MOAS, and eC-SSRS).

11.5.7. Visit 6 (Week 15 ± 3 days)

- Record concomitant medications.
- Perform physical and neurological examination.
- Obtain vital signs and body weight.
- For females of childbearing potential, obtain sample for urine pregnancy test (to be confirmed with serum pregnancy test if positive).
- Record LAEP.
- Record AEs.
- Dispense study drug.
- Collect study drug.
- Record any ESL dose change since the last study visit.
- Record any AED dose change since the last study visit.
- Collect paper seizure diary.
- Distribute paper seizure diary.
- Review seizure diaries.

- Administer the eC-SSRS questionnaire.

11.5.8. Telephone Call 2 (Week 17 ± 3 days)

- Record AEs.
- Record any ESL dose change since the last study visit.
- Record any AED dose change since the last study visit.

11.5.9. Visit 7 and Visit 8 (Week 19 ± 3 days and Week 23 ± 3 days)

- Record concomitant medications.
- Perform physical and neurological examination (Visit 8 only).
- Obtain vital signs and body weight.
- For females of childbearing potential, obtain sample for urine pregnancy test (to be confirmed with serum pregnancy test if positive).
- Record LAEP.
- Record AEs.
- Dispense study drug.
- Collect study drug.
- Record any ESL dose change since the last study visit.
- Record any AED dose change since the last study visit.
- Collect paper seizure diary
- Distribute paper seizure diary
- Review seizure diaries.
- Administer the eC-SSRS questionnaire.

11.5.10. End of Maintenance/End of Study: Visit 9 (Week 27 ± 3 days)

- Record concomitant medications.
- Perform physical and neurological examination.
- Obtain vital signs and body weight.
- Perform a 12-lead ECG.
- For females of childbearing potential, obtain blood for serum β-hCG.
- Obtain blood sample and urine sample for clinical laboratory testing (including thyroid panel).
- Record LAEP.
- Record AEs.

- Dispense study drug if needed for taper (Note: Subjects who elect to continue on commercially available drug will not be dispensed additional ESL at this visit. Subjects who elect to discontinue ESL will be provided sufficient ESL to accommodate the appropriate taper regimen.)
- Collect study drug.
- Record any ESL dose change since the last study visit.
- Record any AED dose change since the last study visit.
- Collect paper seizure diary
- Distribute paper seizure diary
- Review seizure diaries.
- Administer questionnaires (EQ-5D, CGI-I, PGI-C, QOLIE-31, POMS-SF, NDDI-E, MOAS, and eC-SSRS).
- Ensure return of watch and data collection device.

11.5.11. Early Discontinuation Visit

Subjects who withdraw prior to the EOS visit should have an early discontinuation visit (EDV) within 72 hours. Every effort should be made for all subjects prematurely discontinuing the study drug, regardless of cause, to undergo final evaluation described below:

- Record concomitant medications.
- Perform physical and neurological examination.
- Obtain vital signs and body weight.
- Perform a 12-lead ECG.
- For females of childbearing potential, obtain blood for serum β-hCG.
- Obtain blood and urine sample for clinical laboratory testing (including thyroid panel).
- Record LAEP.
- Record AEs.
- Collect study drug.
- Record any AED dose change since the last study visit.
- Collect paper seizure diary
- Distribute paper seizure diary
- Review seizure diaries.
- Administer questionnaires (EQ-5D, CGI-I, PGI-C, QOLIE-31, POMS-SF, NDDI-E, MOAS, and eC-SSRS).
- Dispense study drug if needed for taper.
- Ensure return of watch and data collection device.

11.5.12. Follow-up Visit: Visit 10 or Telephone Call 3 (Week 31 ± 7 days)

- Record AEs.
- Record concomitant medications.
- Review paper seizure diary.

12. SAFETY REPORTING

12.1. Definitions

12.1.1. Adverse Events

An AE is any untoward medical occurrence temporally associated with the use of a drug in humans, whether or not considered drug related.

Untoward medical occurrences that occur between the time of signing the ICF and first drug administration are pre-treatment events. Those that occur after first administration of study drug are considered AEs.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions.

In this study, seizures should not routinely be considered as AEs. Individual seizures (including clusters of seizures and status epilepticus) which are sufficiently severe to require intervention beyond what is usual for the subject or hospitalization may be recorded as AEs. Worsening of seizures (either in severity, pattern, type, or frequency) and injury or other adverse consequences of seizures should be recorded as AEs.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

12.1.2. Serious Adverse Events

A SAE is an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, or blood dyscrasias.

The term “severe” is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 12.3); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious,” which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

SAE criteria information will be captured on the CRF.

12.2. Objective Findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then record the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) as the AE.

Clinical laboratory test results will be reviewed by the Investigator. The Investigator must determine the clinical significance of all out of range values. Clinical laboratory tests with possibly drug related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator. The Investigator will document that he/she has reviewed laboratory tests (for paper reports: initial and date all pages; for electronic reports: document in electronic system or add separate comment to CRF).

Clinical Laboratory Tests Outside the Normal Range: Any value outside the normal range will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether or not the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during screening is indicated as clinically significant and is not covered by the inclusion criteria in Section 8.1, the subject will not be allowed into the study. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the EOS/EDV Visit, this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalised or stabilised.

All on-site ECG tracings will be reviewed by the Investigator. The Investigator must determine the clinical significance of all abnormal ECGs. ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the discretion of the Investigator. ECG tracings will be initialed and dated on all pages by the Investigator.

12.3. Collection and Recording of Adverse Events

All pre-treatment events and AEs must be recorded in the subject's study records/source documents. All pre-treatment events must be recorded on the CRF. All AEs must be recorded on the CRF from first dose administration through the final study visit. All SAEs must be recorded on the CRF from the time informed consent/assent is obtained through the final study visit.

All AEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

Each AE is to be evaluated for duration, severity, frequency, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. Definitions for severity, frequency, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below.

The severity of AE:

- **Mild** – Ordinarily transient symptoms that do not influence performance of subject's daily activities. Other treatment is not ordinarily indicated.
- **Moderate** – Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Other treatment may be necessary.
- **Severe** – Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue the study, and other treatment may be necessary.

The frequency of AE:

- **Once** – an isolated episode.
- **Intermittent** – occurs on 2 or more separate occasions.
- **Continuous** – does not abate from date of onset to date of resolution.

The action taken with the study treatment:

- **Drug Interrupted** – Study drug stopped temporarily.
- **Drug Withdrawn** – Study drug stopped permanently.
- **Dose Reduced.**
- **Dose Increased.**
- **Dose Not Changed.**
- **Not Applicable.**
- **Unknown.**

The outcome of the AE:

- **Recovered/Resolved.**
- **Recovering/Resolving.**

- **Not Recovered/Not Resolved.**
- **Recovered/Resolved with Sequelae.**
- **Fatal.**
- **Unknown.**

The causal relationship of the AE to the study treatment:

- **Not related**
  - **Not related** – Improbable temporal relationship and is plausibly related to other drugs or underlying disease.
- **Related**
  - **Possible** – occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
  - **Probable** – occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
  - **Definite** – occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The adverse event should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The Medical Monitor is the initial contact person for protocol-related questions or discussion of AEs. The contact information for the Medical Monitor as well as other emergency contact information can be found in Table 1 of this protocol.

12.4. Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor:

- SAE.
- Pregnancy.

Emergency contact information can be found in Table 1.

12.4.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of a SAE that occurs in a study subject after obtaining informed consent through 30 days following the last dose of the study medication, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs must be recorded on the CRF and the data recorded should agree with that on the SAE form.

SAEs will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

In addition to the initial telephone notification, an initial SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to PPD Pharmacovigilance

(PPD-PVG) within 1 business day of the Investigator or study center staff becoming aware of the event. The SAE form must be signed by the Investigator or appropriate designee. PPD-PVG provides the SAE form used to report SAEs.

The Sponsor or designee will promptly notify all study centers and Investigators of a SAE that is determined to be expedited to the Regulatory Authorities in accordance with applicable law(s) and regulation(s). These SAEs must be promptly reported to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the Principal Investigator or the appropriate person at the study center if required per IRB/IEC guidelines.

If an SAE is reported after participation of the study, the Investigator or an authorized delegate should report SAEs "spontaneously" to PPD-PVG if considered at least possibly related to the study drug.

12.4.2. Pregnancy

Pregnancies that occur from the time that informed consent is signed through 30 days following the last dose of the study medication will be collected and reported on the Pregnancy Event Form.

If a subject or a subject's partner becomes pregnant during the course of the study, they will be instructed to report the pregnancy to the Investigator (see below). All female pregnant subjects will be instructed to commence discontinuation of the study medication. Further, the subject (or female partner of male subject) will be requested to return promptly/within 48 hours of the first notification of pregnancy to the study center and undergo a serum/urine pregnancy test, as confirmation of pregnancy. If positive, the female pregnant subject will no longer receive any additional study medication. All pregnancies, whether or not the subject received any additional study medication, will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

To report a pregnancy, the Pregnancy Event Form must be completed and sent via fax to PPD- PVG within 1 business day of the Investigator or study center staff becoming aware of the pregnancy. The Sponsor provides the Pregnancy Event Form.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other AEs were detected.

13. TERMINATION OF SUBJECT FROM STUDY

Subjects may terminate the study participation at any time for any reason.

Subjects may be discontinued from the study at any time for any of the following reasons:

- Adverse event.
- Lack of efficacy (specify).
- Withdrawal by subject (specify).
- Withdrawal by Investigator (specify).
- Protocol deviation (specify).
- Study terminated by Sponsor.
- Death.
- Pregnancy (subject or subject's partner).
- Other (specify).

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study.

Subjects may discontinue the study at any time due to worsening of seizures, intolerability, or other reasons.

Subjects who discontinue the study will undergo taper of study drug, unless abrupt discontinuation of the drug is required in response to an AE (eg, rash).

Subjects who experience an intolerable AE at the lowest dose, or who are unwilling to attempt a dose reduction within the allowed range, will be discontinued from the study.

The reason and information for study drug discontinuation will be recorded on the appropriate CRF.

Subjects who prematurely terminate the study participation will not be replaced.

Every effort should be made for all subjects prematurely discontinuing the study drug, regardless of cause, to undergo final evaluation procedures described in Section 11.5.11.

14. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this study center or at multiple centers for safety or administrative reasons at any time while safeguarding that early termination does not compromise subjects' safety or well-being. In particular, a study center that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the study center closed for whatever reason, all documentation must be returned to the Sponsor or its representative.

If, in the opinion of the Investigator, clinical observations suggest it may be unsafe to continue, the Investigator may terminate part or the entire study after consultation with the Sponsor.

15. STATISTICS

15.1. Sample Size

Sample size is calculated based on the precision (a half width of the 95% confidence interval [CI]) for the estimate of the completion rate as assumed as below and is used the Normal approximation to the Binomial distribution.

Arm 1 (first add-on): Assuming a completion rate of 60% at 24 weeks of the Maintenance Phase for Arm 1, to show the lower limit of the 95% CI in the rate to be 50% (50%, 70%), the sample size is estimated at approximately 93 subjects.

Arm 2 (later add-on): Assuming the completion rate of 50% at 24 weeks of the Maintenance Phase for Arm 2, to show the lower limit of the 95% CI in the rate to be 40% (40%, 60%), the sample size is estimated at approximately 97 subjects.

Total estimated subject enrollment is approximately 190 subjects.

15.2. Analysis Populations

The safety population will consist of all subjects who have taken any study medication and will be used for all analyses except efficacy analyses.

The modified intent-to-treat (mITT) population will include subjects who are in the safety population and have available seizure data. The mITT population will be used for efficacy analyses.

15.3. Data Analysis

The Statistical Analysis Plan provides details on the statistical methods planned for this study and will be finalized prior to the database lock. Statistical summaries described in sections below will primarily be provided for all subjects (ie, overall summary) in the analysis populations of interest unless otherwise stated.

All endpoints will be summarized descriptively for Arm 1 and Arm 2 separately. There will be no statistical comparisons between Arm 1 and Arm 2.

For the efficacy endpoints, baseline will be defined as the seizure data for the longest available period up to 3 months prior to screening from seizure history and from screening to first dose of study medication from the paper seizure diary.

For all other endpoints, baseline will be defined as the last non-missing measurement taken prior to the first dose of study drug administration.

15.3.1. Subject Disposition

Subject disposition will be summarized and presented for the number and percentage of subjects, who were screened, screen-failed, completed the study, and discontinued early (including reasons for discontinuations).

15.3.2. Drug Exposure

The number of doses taken as well as the extent of exposure will be summarized with descriptive statistics and presented. For each subject, the number of doses taken will be computed. The extent of exposure will be computed as the number of days from the first exposure to study drug to the last exposure to study drug, ignoring missing days. Average daily dose will also be calculated.

15.3.3. Important Protocol Deviations

Important protocol deviations (IPDs) will be identified and documented based on a review of potentially IPDs. The potentially IPDs will be identified shortly before database lock, either through programmatic checks of study data (eg, inclusion/exclusion criteria violations), as well as through review of selected data listings (eg, Investigator comments, concomitant medications). The potentially IPDs to be reviewed include, but are not limited to, subjects who:

- Did not meet inclusion/exclusion criteria or eligibility was not adequately verified.
- Received any prohibited concomitant medication.
- Developed study withdrawal criteria but were not withdrawn.

Individual IPDs will be presented in a data listing. The number and percentage of subjects with IPDs will be summarized by type of deviation as categorized above.

15.3.4. Demographics and Baseline Characteristics

Demographics, including (age, gender, race, and ethnicity where applicable), and other baseline characteristics collected at screening, such as height, weight, body mass index, and disease conditions will be summarized using descriptive statistics. These data will be presented as a listing.

15.3.5. Primary Analysis

The proportion of subjects completing 24 weeks adjunctive therapy during Maintenance Phase and the 95% CI will be calculated for Arm 1 and Arm 2 separately.

15.3.6. Efficacy Analyses

All efficacy endpoints will be summarized descriptively in this study. Changes in efficacy parameters will be calculated with reference to the baseline, defined as the seizure data for the longest available period up to 3 months prior to screening from seizure history and from screening to first dose of study medication from the paper seizure diary.

All seizure related endpoints will be calculated based on the data from the paper diary.

Seizure frequency will be standardized to 28-day rate. The SSF and changes from baseline will be summarized during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.

Two responder rates (50%, and 75% responder rates) are defined as subjects who have ≥ 50%, and subjects who have ≥ 75% reduction in SSF from baseline, respectively. The proportions of

responders in each rate will be summarized during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.

Relative reduction (%) in SSF from baseline will be calculated during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.

The proportion (%) of seizure-free subjects will be provided during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase.

Time on ESL will be calculated from the first dose to the last known dose of ESL. The median time and 95% CI will be estimated using Kaplan Meier time to event methods. Subjects who were still on ESL at the end of study will be censored at the end of study. Subjects who dropped out of the study while receiving treatment will be an event at the time of the dropout. Change in dosage levels during the treatment period will be ignored.

15.3.7. Other Analyses

15.3.7.1. Neurological Disorders Depression Inventory for Epilepsy Score

The NDDI-E score and change from baseline for each evaluation time point will be summarized descriptively.

15.3.7.2. Profile of Mood States Short-form Score

The POMS-SF scores and changes from baseline for each evaluation time point will be summarized descriptively.

15.3.7.3. Mood States Short-form Score

The MOAS scores and changes from baseline for each evaluation time point will be summarized descriptively.

15.3.7.4. Quality of Life in Epilepsy-Patient-Weighted Score

The QOLIE-31-P scores and changes from baseline for each evaluation time point will be summarized descriptively.

15.3.7.4.1. EuroQol Five Dimensions Questionnaire Score

The EQ-5D scores and changes from baseline for each evaluation time point will be summarized descriptively.

15.3.7.5. Clinical Global Impression of Improvement Score

The CGI-I score for each evaluation time point will be summarized descriptively.

15.3.7.6. Patient's Global Impression of Change Score

The PGI-C score for each evaluation time point will be summarized descriptively.

15.3.8. Safety Analyses

15.3.8.1. Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 or higher. AEs are untoward medical occurrences:

- that occurred on or after the first dose of study medication.
- with a missing start date and a stop date on or after the first dose of study medication, *OR*
- with both a missing start and stop date.

AEs will be summarized by MedDRA system organ class (SOC) and Preferred Term (PT).

The following AEs will be summarized and presented by MedDRA SOC and PT for the Safety population:

- All AEs (including number of events and subject incidence).
- AEs by severity (mild, moderate, severe).
- AEs by relationship to the study treatment (related, or not related).

The following conventions will be followed in summarizing AEs:

- For subject incidence summaries, each subject will be counted only once within each SOC and within each PT.
- If a subject reports more than one AE within a PT and/or a SOC, the AE with the highest known severity within each SOC and within each PT will be included in the summaries by severity.
- For summaries by relationship to the study medication, AEs will be grouped as "related" or "not related." AEs assessed as "possible," "probable," or "definite," will be grouped as "related." If a subject reports more than one AE SOC and PT, and any are related, it will be summarized as related.

Summaries of SAEs, AEs leading to discontinuation or other AE summaries will also be provided if necessary. A listing of AEs, as well as a listing of deaths, SAEs, and AEs leading to discontinuation, will be presented.

15.3.8.2. Adverse Event Profile

The individual LAEP scores and changes from baseline for each evaluation time point will be summarized for each symptom descriptively. The total score and change from baseline will be also summarized. A listing of LAEP will be provided.

15.3.8.3. Clinical Laboratory Assessments

For laboratory parameters with continuous outcomes, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) will be presented. For laboratory parameters with categorical outcomes, the number and percentage of subjects with each outcome will be presented. The number and percentage of subjects with potentially clinically significant

laboratory values will be summarized. The data listings for laboratory parameters will flag values outside of the reference range. Out of reference range findings with codes for clinical significance will be displayed in a separate data listing. Clinical laboratory variables will be summarized descriptively on the actual values and changes from baseline. Shift tables from baseline to the end of this study will be provided for laboratory parameters.

15.3.8.4. Blood Sodium Levels

In addition to descriptive summaries of blood sodium levels and changes from baseline for each assessment time point, the percent of subjects with normal baseline sodium level reaching ≤ 135 mEq/L but > 130 mEq/L, ≤ 130 mEq/L but > 125 mEq/L, ≤ 125 mEq/L, and > 10 mEq/L reduction (ie, < -10 mEq/L) from baseline will be summarized by time point.

15.3.8.5. Electrocardiograms

ECG abnormalities will be presented in a data listing.

15.3.8.6. Vital Signs and Weight

Vital signs (supine systolic and diastolic blood pressures, respiratory rate, pulse rate, and oral temperature) and weight will be summarized using descriptive statistics at baseline and each evaluation visit. Change from baseline will be included in this presentation as well. In addition, a subject incidence (and percentage) of potentially clinically significant vital signs values will be presented.

15.3.8.7. Physical/Neurological Examination

All physical and neurological exam findings at screening will be captured in the medical history and summarized together with the other medical history events. Clinically significant changes from the screening visit will be captured as AEs as appropriate, and summarized together with the other AEs.

15.3.8.8. Concomitant Medications

All medications will be coded using the WHO-DRUG.

Any medications taken during the course of the study, with a start date on or after the date of the first dose of study drug and on or before the date of the last dose of study drug; or with a start date prior to, and an end date on or after, the date of the first dose of study drug, or marked as ongoing, will be considered concomitant medications. Medications that ended prior to the date of the first dose of the study drug will be considered prior medications. The number and percentage of subjects using each concomitant medication will be summarized overall according to the WHO-DRUG Anatomic Therapeutic Chemical (ATC) level and PT. Subjects with multiple uses of a concomitant medication will be counted once by the ATC level and PT.

15.3.8.9. Electronic Columbia-Suicide Severity Rating Scale

The percentage of subjects in each classification class for overall and at each assessment time will be summarized.

15.3.9. Exploratory Analyses

The proportions of concordance in the daily seizure frequency during the 24-weeks of the Maintenance Phase between the watch device and paper diary as well as between the Mate application and paper diary for each subject will be calculated.

SSF during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase will be calculated using the seizure data recorded by the investigational wearable watch device, and MATE application from Empatica. The concordance correlation coefficient (CCC) with 95% confidence interval will be calculated to assess agreement in SSF during the first 12 weeks, the last 12 weeks, and the 24 weeks of the Maintenance Phase between the two Empatica devices and the paper diary.

Scatter plots of the above SSFs using the seizure data recorded by the watch device as well as Mate application by those from the paper diary will be presented to evaluate agreement graphically.

15.3.10. Treatment of Missing Data

Subjects who dropped out before study completion are not to be replaced and all available information obtained from them will be included in the appropriate efficacy and safety summaries to the time of dropout. No imputation is planned for any safety measures.

If the date of the seizure is missing or incomplete and the seizure cannot be allocated to a study period, these data will not be used in the analysis, but will be presented in the subject data listings. If the seizure diary was returned and there was no seizure data available for a particular day during that evaluation period, it will be assumed that the patient had missing seizure data, and the day will be excluded from the calculation of the standardized seizure frequency.

Seizure-related variables will be calculated based on available data. For dropout subjects, their seizure frequency will be derived up to the last period where the subject had data. The last period SSF will be computed based on available data prior to dropout.

16. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL, DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

16.1. Data Collection/Electronic Data Capture

The results from screening and data collected during the study (except clinical laboratory test results) will be recorded via electronic source data collection. The study centers will use an electronic system to record subject data.

This protocol shall incorporate technology to capture source documents and source data electronically consistent with FDA Guidance for Industry "Computerized Systems Used in Clinical Investigations" (May 2007) and FDA Guidance for Industry "Electronic Source Data in Clinical Investigations" (September 2013). All electronic source documentation and data collected in this study shall "meet the same fundamental elements of data quality (e.g. attributable, legible, contemporaneous, original, and accurate) that are expected of paper records."

Sites will use a tablet PC to directly record subject data and clinical observations on electronic forms with a similar look/feel/behavior as paper forms. This permits the collection of both structured and unstructured information including ad-hoc comments, drawings, and relevant clinical notes the investigative site deems important. Information to be originally captured and reviewed electronically shall include but not limited to the details of the subject visit, Medical History, Adverse Events, and Concomitant Medications. The eSource technology platform possesses the ability to immediately validate data, highlight required and dependent data fields, as well as to document discrepancies at the time the data is originally captured. Because this study is using an electronic source record as the original point of data capture, there is no additional data entry step for the site – rather, the electronic source record directly populates the study database.

16.2. Study Monitoring

This study will be monitored from initiation to completion by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with ICH GCP.

16.3. Audits

The study may be subject to audit by the Sponsor/designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. This is dependent on the subject granting consent by signing the ICF. By signing this protocol, the Investigator grants permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study documentation.

16.4. Study Documentation

Study records are comprised of source documents and all other administrative documents, eg, IRB/IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study-specific binder will be provided with instructions for the maintenance of study records.

Source document is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy final report.

16.5. Clinical Laboratory Certification and Normal Values

A central laboratory will be used for analysis for most of the clinical laboratory tests for this study. The central laboratory will provide the Investigator and Sponsor/CRO with laboratory certification(s) and a dated copy of normal range values for the central clinical laboratory selected to analyze clinical specimens. If an exception is granted to use a local laboratory, the Investigator must supply the Sponsor/CRO with laboratory certification, lab director’s curricula vitae and a current, dated copy of normal range values.

17. ETHICAL AND REGULATORY OBLIGATIONS

17.1. Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, ICH GCP, ICH guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The Investigator must sign and return to Sponsor/CRO the "Investigator Approval" page.

The Investigator must provide a copy of current curriculum vitae (including a copy of a current medical license), and financial disclosure information.

The Investigator must sign and return a completed Form Food and Drug Administration (FDA) 1572 "Statement of Investigator" to Sponsor/CRO.

17.2. Institutional Review Board/Independent Ethics Committee

Documented approval for conducting the study from appropriate IRB/IEC will be obtained for all participating study centers prior to initiation of the study, according to ICH GCP, applicable local law(s) and regulation(s). When necessary, an extension, amendment or renewal of the IRB/IEC approval must be obtained and also forwarded to the Sponsor. The IRB/IEC must supply the Sponsor a list of the IRB/IEC membership, and a statement to confirm that the IRB/IEC is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB/IEC approval or favorable opinion of the protocol, ICF and subject recruitment material (if applicable) must be provided to Sponsor/CRO prior to start of the study. The approval or favorable opinion letter must be signed by the IRB/IEC chairman or designee, identify the IRB/IEC name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB/IEC complies with the requirements in 21 Code of Federal Regulations (CFR) Part 56 for a study conducted under a US IND or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining from the IRB/IEC continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not to exceed one year and (if applicable) as otherwise additionally specified by the IRB/IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB/IEC of all SAEs reported by subjects enrolled in the study or other safety information reported from Sponsor/CRO in accordance with applicable law(s) and regulation(s).

17.3. Informed Consent

The ICFs (the ICF provided to all subjects as well as the ICF provided to subjects providing samples for genetic testing) will be approved by the Sponsor/CRO prior to submission to the IRB/IEC. The CRO may provide a template ICF to be qualified by each research facility to conform to local requirements. All ICFs must contain the minimum elements as mandated by ICH GCP, applicable local law(s) and regulations and will be subject to Sponsor/CRO approval as well as IRB/IEC approval.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study, allowed to read the approved ICF and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject understands the implications of participating in the study, the prospective subject will be asked to give consent to participate in the study by signing the ICF. As part of the consent process, each prospective subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. It should be clearly explained to each prospective subject that participation in each and every clinical visit and assessment is expected. The Investigator will provide a copy of the signed ICF to each subject, and will record the date of the informed consent on the CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's consent, the ICF must be revised, submitted to the IRB/IEC for review and approval or favorable opinion. The revised ICF must be used to obtain consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised ICF must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

17.4. Subject Privacy

The Sponsor (or Sponsor representative) or any designees affirm to uphold the subjects confidentiality. The subject will be identified by unique code only; full names will be masked prior to transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations.

17.5. Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB/IEC. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC immediately/within five business days of the occurrence, or in accordance with applicable regulatory requirements.

17.6. Records Retention

The Investigator/the study center must arrange for retention of study records at the study center for at least 15 years from time of participation in the study or longer in accordance with applicable regulations and Sponsor standard operating procedure. The Investigator/site should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the study center when the destruction of documents is permitted.

17.7. Inspection of Records

In the event of an inspection, the Investigator agrees to allow representatives of the Sponsor and its representative and, the regulatory authorities' access to all study records. The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sunovion-sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

17.8. Financial Disclosure

By signing this protocol, the Investigator agrees to provide to the Sponsor prior to start of study accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study.

The Investigator also consents to the transmission of this information to the Sponsor for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

17.9. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

18. REFERENCES

Commission on Classification and Terminology of the International League Against Epilepsy (ILAE). Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981;22:489-501.

Committee for Proprietary Medicinal Products (CPMP). Note for guidance on clinical investigation of medicinal products in the treatment of epileptic disorders. London, England; 22 January 2009 (CHMP/EWP/566/98 Rev. 2).

Dreifuss FE. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia. 1981;22:249-60.

Epilepsy Fact Sheet. World Health Organization (WHO), World Health Organization, Feb 2016 [Accessed 17 Oct 2016]. http://www.who.int/mediacentre/factsheets/fs999/en/

FDA Guidance for Industry. Computerized Systems Used in Clinical Investigations, May 2007. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.pdf. Accessed 10 February 2017.

FDA Guidance for Industry. Electronic Source Data in Clinical Investigations. September 2013. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf. Accessed 10 February 2017.

19. INVESTIGATOR APPROVAL

I have read the protocol, SEP093-701, "Efficacy and Safety of Eslicarbazepine Acetate as First Add-on to Levetiracetam or Lamotrigine Monotherapy or as Later Adjunctive Treatment for Subjects with Uncontrolled Partial-onset Seizures: A Multicenter, Open-label, Non-randomized Trial" Version 3.01, and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

20. APPENDIX I. CLINICAL LABORATORY TESTS

Clinical Safety Panel

HEMATOLOGY: (Differential reported as % and absolute value)

Hemoglobin, Hematocrit, Platelet Count, Red Blood Cell Count, WBC - Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Glucose, Magnesium (Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid, Albumin

URINALYSIS: Blood, Glucose, Ketones, Leukocyte esterase, Microscopic examination, Nitrites, pH, Protein

THYROID PANEL: Free T3, Free T4, TSH

RENAL FUNCTIONING: Creatinine clearance (calculated glomerular filtration rate using the Cockcroft-Gault equation) at Screening only.

URINE DRUG SCREENING: Amphetamines, Barbiturates, Benzodiazepines, Cocaine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone

OTHER TESTS: Serum Pregnancy (β-hCG) in female subjects of childbearing potential, only; Urine Pregnancy Test (in female subjects of childbearing potential only, on-site testing)

Laboratory reports will be initialed and dated on all pages by the Investigator listed on the Form FDA 1572 (MD or DO). Laboratory test results will be reviewed by the Investigator as they become available. The Investigator must determine the clinical significance of all out-of-range lab values (except drug screens). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

21. APPENDIX II. CARDIAC SAFETY MONITORING

1. Requirements for Testing

Electrocardiogram equipment and supplies will be provided by the site.

- All 12-lead ECGs will be recorded in the same manner.
- The study center personnel must be adequately trained in performing ECGs.
- To the extent possible, the same ECG machine and personnel should be used to acquire a subject's ECGs throughout the period of their participation in the study.
- ECGs will be recorded with at least one 10-second single-lead tracing recorded from Lead II.

2. Subject Restrictions and Instructions

- Prior to ECG acquisition, the subject will have rested 10 minutes in the supine position and will remain so until the ECG is obtained.

3. Reporting

- It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility or continuance in the study. Abnormalities require comment such as "not clinically significant" or "clinically significant." Typically, clinically significant events will be reported as adverse events.
- ECGs will be reviewed, signed and dated by the Investigator listed on the Form FDA 1572 (MD or DO) after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.
- The ECG tracing will be kept with subject's source documentation and/or CRF unless it is specified otherwise. The original ECG will be retained at the study center and the Sponsor may collect a copy.

22. APPENDIX III. SAMPLE DAILY SEIZURE DIARY

Subjects (or their caregiver) will be required to complete a daily seizure diary, regardless whether a seizure has occurred for a given day. A daily seizure diary will be provided to subjects/caregivers (sample provided below).

SUNOVION	**Protocol: SEP093-701**	**Subject #:** _____-_____	**Subject Initials:** ____-____-____

Seizure Code	**Seizure Type**	**Seizure Description** *(to be completed by PI with the patient/caregiver)*
A	Simple partial	
B	Complex partial	
C	Partial with Secondary Generalization	
D	Other	

SUNOVION	**Protocol: SEP093-701**	**Subject #:** _____-_____	**Subject Initials:** ____-____-____

Daily Seizure Record

DATE (DD/MMM/YYYY)	**SEIZURES**				
	Did I have any seizures today?	**Seizure code with # of Seizures (per code)**			
__ /___/____	☐ **Yes** ☐ **No**	**A**	**B**	**C**	**D**
__ /___/____	☐ **Yes** ☐ **No**	**A**	**B**	**C**	**D**
__ /___/____	☐ **Yes** ☐ **No**	**A**	**B**	**C**	**D**
__ /___/____	☐ **Yes** ☐ **No**	**A**	**B**	**C**	**D**
__ /___/____	☐ **Yes** ☐ **No**	**A**	**B**	**C**	**D**