



Protocol No. 093-050

Long-Term Eslicarbazepine Acetate Extension Study

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2. SYNOPSIS

Name of Sponsor/Company: Sunovion Pharmaceuticals Inc.
Name of Study Drug: Eslicarbazepine acetate
Name of Active Ingredient: Eslicarbazepine acetate
Title of Study: Long-Term Eslicarbazepine Acetate Extension Study
Study Center(s): Approximately 150 investigative US and ex-US sites are planned to enroll subjects.
Principal Investigator(s): To be determined. Investigator(s): To be determined.
Phase of Development: III
Primary Objective: To evaluate the 1-year and post-1-year safety and tolerability of eslicarbazepine acetate flexible dosing within the range of 800 mg to 2400 mg in subjects with partial epilepsy who have participated in an 18-week double-blind eslicarbazepine acetate monotherapy study (Protocols 093-045 or 093-046). Secondary Objectives: <ul style="list-style-type: none">• To evaluate the maintenance of the therapeutic effects of eslicarbazepine acetate over a 1-year and post-1-year open-label period.• To evaluate the health-related quality-of-life, suicidality, and depressive symptoms over a 1-year and post-1-year open-label period.
Study Design: The present study is a long-term, multicenter, open-label, safety extension study in male and female subjects (aged 16 to 70 years, inclusive) with partial onset seizures who have just completed, discontinued, or exited the 18-week treatment phase of Protocols 093-045 or 093-046. The initial study duration is 1-year with the option of continuing study drug treatment post-1-year until a subject discontinues study, the study drug becomes clinically available in the subject's locale, or the sponsor terminates the study drug clinical development program. This study will evaluate the safety and maintenance of effect of long-term eslicarbazepine acetate treatment at flexible doses in the range of 800 mg to 2400 mg once-a-day (QD) over a 1-year and a post-1-year period. Subjects who enter the present study will receive a starting dose of 1600 mg QD of eslicarbazepine acetate, orally for 1 week at the start of the 1-year period. The starting dose for subjects who had a dose reduction during participation in studies 093-045 or 093-046 will be 1200 mg and not 1600 mg. At the end of this 1-week period, subjects will be allowed to continue at this dose or at the discretion of the Investigator, increase, or decrease dose as necessary for efficacy or tolerability reasons. There is no limit on the number of dose increments or reductions during the study, however, all dose increases or reductions should occur in steps of 400 mg and a minimum of 1 week must pass between one dose change and the next. Dose reductions of more than 400 mg are allowed at the discretion of the Investigator for a documented safety reason. The maximum allowed dose of eslicarbazepine acetate is 2400 mg QD and the minimum allowed dose is 800 mg QD in this study. Subjects who continue into the post-1-year part of the study will continue to receive the same dose of study drug that they received at Visit 7 (end of 1-year of treatment). The same dosing rules as in the 1-year part of the study are applicable in the post-1-year part.

Subjects with a clinically significant increase in seizure frequency, duration, or severity, who have not responded to or did not tolerate an increase in dose of study drug, may be started on an additional antiepileptic drug (AED) during both the 1-year and post-1-year parts of the study. A maximum of two additional AEDs to control seizures will be allowed, however oxcarbazepine will not be allowed. If, after the addition of the second additional AED, the subject experiences an adverse event, the dose of eslicarbazepine acetate should be reduced before changing the dose of the concomitant AED. In addition, for subjects with a vagal nerve stimulator (VNS), the device setting may be changed as needed.

Subjects who require doses outside of the 800 mg QD to 2400 mg QD range or more than 2 additional AEDs during the 1-year or post-1-year parts of the study will be discontinued from study participation.

Physicians may prescribe lorazepam for rescue use. Diazepam (rectal gel) as an emergency medication will be provided by the sponsor (via prescription from local physician). In countries where lorazepam and/or diazepam rectal gel are not available, alternate treatments are allowed per Appendices XII and XIII.

Number of Subjects (Planned): Up to 348 subjects (up to 174 subjects each from Protocols 093-045 and 093-046) may be enrolled.

Diagnosis and Main Criteria for Inclusion: Subjects with partial onset seizure epilepsy not well controlled with one or two AEDs and who have completed, discontinued, or exited from Protocols 093-045 or 093-046 are eligible to participate. Subjects who discontinued from Protocols 093-045 or 093-046 for reasons other than reaching exit criteria may be eligible if there is no safety concern. Subjects must have completed at least the first 3 weeks of the 18-week double-blind treatment period of these studies to enroll in this study. Subjects must enter the present study immediately upon completion, discontinuation, or exit from Protocols 093-045 or 093-046.

Study Drug, Dosage and Mode of Administration: During both the 1-year and post-1-year parts of the study, eslicarbazepine acetate, 800 mg, 1200 mg, 1600 mg, 2000 mg, or 2400 mg per day; oral administration once daily in the morning with water, with or without food. Administered as a combination of 400 mg tablets of eslicarbazepine acetate. Subjects receiving 800 mg eslicarbazepine acetate per day will receive two 400 mg tablets per day; 1200 mg will receive three 400 mg tablets per day; 1600 mg will receive four 400 mg tablets per day; 2000 mg per day will receive five 400 mg tablets per day; and 2400 mg will receive six 400 mg tablets per day. All tablets are to be taken simultaneously, when applicable.

Duration of Treatment: Total duration of treatment is 1-year and beyond (post-1-year). Subjects may discontinue the study at any time due to worsening of seizures, tolerability, or other reasons.

Reference Therapy, Dosage, and Mode of Administration: None.

Criteria for Evaluation:

1-Year Safety Endpoints:

- Clinical evaluations (adverse events, vital signs, orthostatic effects, physical examination, body weight, and 12-lead electrocardiograms [ECGs]).
- Clinical laboratory evaluations (serum chemistry, hematology and urinalysis), high-density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, and triglycerides), coagulation testing (prothrombin time [PT]/international normalized ratio [INR], and partial thromboplastin time [PTT]), bone turnover markers (serum 25-hydroxyvitamin D [25-OHD], parathyroid hormone [PTH], osteocalcin, bone-specific alkaline phosphatase, and urinary

N-telopeptides of type I collagen cross-links [NTx]).

- Proportion (%) of subjects with increase of body weight $\geq 7\%$.
- Proportion (%) of subjects with normal baseline blood sodium reaching levels of ≤ 135 mmol/L, ≤ 130 mmol/L, and ≤ 125 mmol/L.
- Columbia Suicidality Severity Rating Scale (C-SSRS).

1-Year Efficacy Endpoints:

- Time on eslicarbazepine acetate monotherapy.
- Seizure frequency reduction from baseline period (Visit 1 to 2) of Protocols 093-045 or 093-046.
- Responder rate (proportion [%] of subjects with a $\geq 50\%$ reduction of seizure frequency from baseline period [Visit 1 to 2] of Protocols 093-045 or 093-046).
- Proportion (%) of subjects who are seizure-free during the 1-year period (determined in 12-week intervals).
- Seizure frequency by seizure type.
- Completion rate (proportion [%] of subjects completing the 1-year treatment).
- Treatment retention time (time to withdrawal due to lack of efficacy or adverse events).
- Change in total score from Visit 2 (Day 0) of Protocols 093-045 or 093-046 to end of study treatment (Visit 7, Month 12) in 31-Item Quality of Life in Epilepsy (QOLIE-31).
- Change in total score from Visit 2 (Day 0) of Protocols 093-045 or 093-046 to end of study treatment (Visit 7, Month 12) in Montgomery-Asberg Depression Rating Scale (MADRS).
- Change in total score from Visit 2 (Day 0) of Protocols 093-045 or 093-046 to end of study treatment (Visit 7, Month 12) in MADRS in those subjects with a MADRS score of ≥ 14 at screening visit of the present study.

Post 1-year Endpoint:

- Fraction of subjects who completed treatment at each visit post-1-year.

Statistical Methods:

Populations for Analysis: The intent-to-treat (ITT) population will consist of all subjects who have taken any study medication. The ITT population will be used for safety and efficacy analyses.

Safety Analysis: Safety outcomes will be analyzed descriptively. Safety variables will include adverse events, vital sign measurements, orthostatic effects, clinical laboratory evaluations (serum chemistry, hematology, and urinalysis), thyroid function, lipid levels, coagulation testing, and bone turnover markers, body weight, blood sodium levels, ECG readings, and C-SSRS.

Efficacy Analysis: All efficacy endpoints will be summarized descriptively for the treatment group in Protocol 093-050. Time on eslicarbazepine acetate monotherapy will be calculated from the first monotherapy dose in 093-045 or 093-046 to the last known dose of eslicarbazepine acetate monotherapy in 093-050. Median time and 95% CI will be estimated using Kaplan Meier time to event

methods. Subjects who were still on eslicarbazepine acetate monotherapy at the end of study will be censored at known dose. Changes in efficacy parameters will be calculated with reference to the baseline period of Protocols 093-045 or 093-046.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Full Form
AE	Adverse experience/event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CNS	Central nervous system
eCRF	Electronic case report form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of Variation
ECG	Electrocardiogram
EOS	End of study
ET	Early termination
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
HDL	High-density lipoprotein
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IPD	Important protocol deviation
IRB	Institutional Review Board
ITT	Intent-to-treat
LDL	Low-density lipoprotein
MAOI	Monoamine oxidase inhibitor
MADRS	Montgomery-Asberg Depression Scale
MEC	Medical Event Calendar
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
NTx	N-Telopeptides of type I collagen cross-links
25-OHD	25-Hydroxyvitamin D
OTC	Over-the-counter
PR	Time between P wave and QRS in electrocardiography
PT	Prothrombin time
PTH	Parathyroid hormone
PTT	Partial thromboplastin time
QD	Once-a-day
QOLIE-31	31-Item Quality of Life in Epilepsy

Abbreviation	Full Form
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
SAE	Serious adverse experience/event
SOC	System organ class
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
VGSC	Voltage-gated sodium channel
®	Registered trademark (registered in United States Patent and Trademark Office)

For the purposes of standardization, the following definitions will be used:

- **Screened Subject:** Any subject who signed the study specific informed consent and completed at least one study related procedure.
- **Screen Failure Subject:** 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 did not achieve on-study status.
- **Study Drug (or study medication):** Term to cover investigational drug (eslicarbazepine acetate). Eslicarbazepine acetate is also referred to as SEP-0002093 or BIA 2-093 in other related documents. The study drug will be described as eslicarbazepine acetate in this document.
- **Active Treatment Phase:** The period of the study in which the study drug is administered.
- **On-Study Subject:** Any subject who passed screening and received study drug; and/or had significant procedures as defined by the protocol (eg, biopsy, genetic profiling). Note: Significant procedures may require subjects to be considered on-study as these procedures may drive scheduling of interim monitoring visits and management of electronic Case Report Forms (eCRFs).
- **Completed Subject:** Any subject who participated throughout the duration of the study, up to and including the last in-clinic visit.
- **Early Termination Subject:** Any subject who was successfully screened and achieved on-study status, but did not complete the study.

5. INTRODUCTION

Epilepsy is a brain disorder resulting from dysfunction in neuronal signaling and physically manifested foremost as seizures. Illness, head trauma and environmental and genetic factors contribute to the etiology of epilepsy. The disorder affects all age groups, may be chronic and in most cases requires long-term therapy.

The prevalence of epilepsy worldwide is estimated to be approximately 50 million with a worldwide incidence rate of 50 to 100 per 100,000 people.¹ In the United States (US) more than 2 million people have active epilepsy.² About 25% to 30% of these patients have intractable epilepsy that does not respond to conventional antiepileptic drug (AED) treatments.²

Eslicarbazepine acetate, (S)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide, is structurally similar to two currently marketed AEDs, carbamazepine and oxcarbazepine. However, a key molecular difference at the 10, 11 position of eslicarbazepine acetate confers on it a unique metabolic pathway absent of epoxide formation and autoinduction that may contribute to side effects observed with the above mentioned AEDs.

Physiologically, eslicarbazepine acetate is a voltage-gated sodium channel (VGSC) blocker. The VGSCs are transmembrane proteins found in neurons of the central nervous system (CNS) and responsible for the conduction of electrical impulses from neuron to neuron. Deactivation of VGSC is associated with altered states of neuronal excitability and has therapeutic advantage in treating disorders such as epilepsy.³⁻⁵ Genetic mutations in certain VGSC isoforms have been linked to development of epilepsy.⁶⁻⁸

Approximately 1700 subjects have been exposed to eslicarbazepine acetate in 22 Phase I, 5 Phase II, and 3 Phase III completed clinical studies. These studies have included healthy volunteers, adult and pediatric subjects with partial onset epilepsy, and adults with bipolar disorder. Total daily doses of eslicarbazepine acetate ranged from between 20 mg to 3600 mg in adults and 5 to 30 mg/kg/day in children given as single or multiple doses from 1 day to up to 1 year. The longest exposure to eslicarbazepine acetate is approximately 38 months as add-on therapy in epileptic subjects in an open-label Phase 3 extension study. The maximum tolerated multiple oral dose of eslicarbazepine acetate in healthy adult subjects was 2400 mg QD.

Three Phase III placebo-controlled clinical studies have been conducted using eslicarbazepine acetate as adjunctive therapy in 1,050 randomized adult subjects with partial onset seizures refractory to treatment with 1 to 3 concomitant AEDs. Doses of 800 and 1200 mg/day significantly reduced ($p < 0.0001$) the number of seizures compared to placebo over a 12-week maintenance period in all studies. In one open-label long-term extension study (Part II of BIAL Studies SCO/BIA-2093-301) adjunctive eslicarbazepine acetate therapy was shown to reduce seizures and was well tolerated over a one-year period.

In April 2009 the Committee for Medicinal Products for Human Use (CHMP) approved Zebinix™ (eslicarbazepine acetate) 400 mg, 600 mg, 800 mg, tablets as adjunctive therapy in adults with partial-onset seizures with or without secondary generalization. The applicant for this medicinal product was BIAL - Portela & Ca, S.A.

The results with eslicarbazepine acetate as adjunctive treatment to other AEDs suggest that the compound may be efficacious and well tolerated when administered as a monotherapy and that these effects may be sustained over a one-year period. Clinical experience with oxcarbazepine (a sodium channel blocker structurally similar to eslicarbazepine acetate) has shown that higher doses of oxcarbazepine can be tolerated as monotherapy than in combination with other AEDs. These findings resulted in an approved dose range for oxcarbazepine up to 1200 mg as adjunctive therapy, but up to 2400 mg as a monotherapy.⁹⁻¹³ Doses of eslicarbazepine acetate up to 2400 mg were well tolerated as monotherapy in patients with bipolar disorder (unpublished results).

Subjects who participated in the double-blind 18-week withdrawal to monotherapy studies (Protocols 093-045 and 093-046) with eslicarbazepine acetate will be eligible to participate in this long-term extension study. This study will determine if the efficacy and safety of eslicarbazepine acetate monotherapy is sustained over a one-year period.

The present study design has carefully considered possible long-term risks and benefits for the participating subjects. In cases where subjects experience an increase in seizure severity or frequency, an increase in the dose of study drug (in 400 mg increments of up to a maximum of 2400 mg QD) is allowed. After the attempt to increase the dose of study drug, the addition of up to two AEDs will be allowed to control seizures. Furthermore, in subjects who do not tolerate the assigned dose there will be the possibility of dose reductions (in 400 mg steps) to a minimum of 800 mg QD. If, after the addition of the second AED, the subject experiences an adverse event, the dose of eslicarbazepine acetate should be reduced before changing the dose of the concomitant AED.

The available data with eslicarbazepine acetate show that the drug has potential advantages.^{14,15} The QD administration may lead to increased convenience for subjects and improved compliance with treatment. Furthermore, the drug shows little or no enzyme induction, no toxic metabolites, less sedation or hyponatremia, and does not lead to weight gain so that switching from other AEDs to eslicarbazepine acetate may be beneficial for the study participants.

Long-term data from one study demonstrate the maintenance of effect and safety over the course of one year (Part II of BIAL Study SCO/BIA-2093-301). A total of 314 subjects received approximately 880 mg QD (median 800 mg) of eslicarbazepine acetate for 6 to 12 months in this study. Subjects showed significant improvements from baseline in health-related quality of life and depressive symptoms. The most frequent treatment-emergent adverse events (TEAE) reported in this study were headache, dizziness, diplopia, and nasopharyngitis (5 to 10%). Eleven subjects (3.5%) reported a TEAE that led to discontinuation.

Eslicarbazepine acetate is also referred to as SEP-0002093 and BIA 2-093 in other related documents. In this document, the term eslicarbazepine acetate will be used to describe the study drug. Please refer to the current Investigator's Brochure for additional information.

6. STUDY OBJECTIVES AND PURPOSE

This study will confirm the long-term safety and maintenance of effect of eslicarbazepine acetate (flexible dose range of 800 mg to 2400 mg) in subjects with partial onset seizures, with or without secondary generalization, not well controlled by current AEDs.

6.1. Primary Objective

To evaluate the 1-year and post-1-year safety and tolerability of eslicarbazepine acetate flexible dosing within the range of 800 mg to 2400 mg in subjects with partial epilepsy who have participated in an 18-week double-blind eslicarbazepine acetate study (Protocols 093-045 or 093-046).

6.2. Secondary Objectives

- To evaluate the maintenance of the therapeutic effects of eslicarbazepine acetate over a 1-year and post-1-year open-label period.
- To evaluate the health-related quality of life, suicidality, and depressive symptoms over a 1-year and post-1-year open-label period.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

The present study is a long-term, multicenter, open-label, safety extension study in male and female subjects (aged 16 to 70 years, inclusive) with partial onset seizures who have just completed, discontinued, or exited the 18-week treatment phase of Protocols 093-045 or 093-046. The initial study duration is 1-year with the option of continuing study drug treatment post-1-year until a subject discontinues study, the study drug becomes clinically available in the subject's locale, or the sponsor terminates the study drug clinical development program.

This study will evaluate the safety and maintenance of effect of long-term eslicarbazepine acetate treatment at flexible doses in the range of 800 mg to 2400 mg QD over a 1-year and a post-1-year period.

Subjects who exit Protocols 093-045 or 093-046 by meeting any of the protocol-defined exit criteria are eligible to participate in this study. Subjects who discontinue from Protocols 093-045 or 093-046 for reasons other than reaching exit criteria may be eligible if there is no safety concern. Subjects must have completed at least the first 3 weeks of the 18-week double-blind treatment period of these studies. Subjects must enter the present study immediately upon completion, discontinuation, or exit from Protocols 093-045 or 093-046.

Subjects who enter the present study will receive a starting dose of 1600 mg QD of eslicarbazepine acetate, orally for 1 week at the start of the 1-year period. **The starting dose for subjects who had a dose reduction during participation in studies 093-045 or 093-046 will be 1200 mg and not 1600 mg.** At the end of this 1-week period, subjects will be allowed to continue at this dose or, at the discretion of the Investigator, increase or decrease dose as necessary for efficacy or tolerability reasons. There is no limit on the number of dose increments or reductions during the study, however, all dose increases or reductions should occur in steps of 400 mg and a minimum of 1 week must pass between one dose change and the next. Dose reductions of more than 400 mg are allowed at the discretion of the Investigator for a documented safety reason. The maximum allowed dose of eslicarbazepine acetate is 2400 mg QD and the minimum allowed dose is 800 mg QD in this study. Subjects who continue into the post-1-year part of the study will continue to receive the same dose of study drug that they received at Visit 7. The same dosing rules as in the 1-year part of the study are applicable in the post-1-year part.

Subjects with a clinically significant worsening of seizures or increase in seizure frequency, who have not responded to or did not tolerate an increase in dose of study drug, may be started on an additional AED during both the 1-year and post-1-year parts of the study. A maximum of two additional AEDs to control seizures will be allowed. However, one of these additional AEDs must not be oxcarbazepine. If, after the addition of the second AED, the subject experiences an adverse event, the dose of eslicarbazepine acetate should be reduced before changing the dose of the concomitant AED. In addition, for subjects with a vagal nerve stimulator (VNS), the device setting may be changed as needed.

Subjects who require doses outside of the 800 mg QD to 2400 mg QD range or more than 2 additional AEDs during the 1-year or post-1-year parts of the study will be discontinued from study participation. See [Figure 7.1-1](#) for a study schematic.

Physicians may prescribe lorazepam for rescue use. Diazepam rectal gel (Diastat[®]¹ [see [Appendix XI](#) for dosing information]) as an emergency medication will be provided by the sponsor (via prescription from local physician). In countries where lorazepam and/or diazepam rectal gel are not available, alternate treatments are allowed per [Appendices XII](#) and [XIII](#).

Study Periods

1-Year Part

Visit 1 (Screening): At the end of the 18-week treatment period or early termination from Protocols 093-045 or 093-046, subjects who choose to enter this study will undergo procedures as outlined in the Schedule of Assessments ([Table 7.1-1](#)). This visit corresponds to Visit 9 (End of Treatment/Early Termination Visit) in Protocols 093-045 or 093-046. Visit 9 assessments from Protocols 093-045 or 093-046 will serve as the baseline assessments for the present study at Visit 1. Subjects will receive a starting dose of 1600 mg QD of eslicarbazepine acetate (**1200 mg QD for subjects who had a dose reduction in Protocols 093-045 or 093-046**).

Visit 2 (Week 1): Subjects will return to the clinic 1 week after Visit 1 for procedures as specified in the Schedule of Assessments ([Table 7.1-1](#)). From this visit onwards, the dose of eslicarbazepine acetate may be increased or decreased at the discretion of the Investigator. There is no limit on the number of dose increments or reductions during the study, however, an increase or decrease in dose should occur in steps of 400 mg. Dose reductions of more than 400 mg are allowed at the discretion of the Investigator for a documented safety reason. A minimum of 1 week must pass between one dose change and the next.

Visits 3 through 6: Subjects will return to the clinic after Visit 2 at 3-week (Visit 3), 2-month (Visit 4), and 3-month intervals (Visits 5 and 6) for procedures as specified in the Schedule of Assessments ([Table 7.1-1](#)).

Visit 7: Subjects will return to the clinic at the end of the 1-year treatment period (3 months after Visit 6 [Visit 7]) for procedures as specified in the Schedule of Assessments ([Table 7.1-1](#)). At this visit subjects may choose to continue treatment with study drug post-1-year. Subjects, who choose to continue study drug post-1-year, will start this part of the study on the same dose of study drug as they received at Visit 7. Subjects who choose not to continue into the post-1-year part of the study will return after 1-week of this visit for EOS/ET procedures (see below).

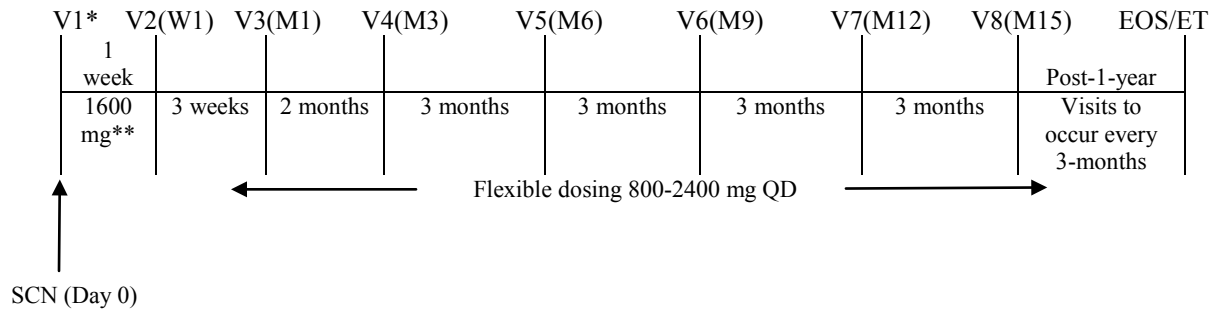
Post-1-Year Part

Visit 8 and onwards (Month 15 onwards): In the post-1-year part of the study subjects will return to the clinic at 3-month intervals for procedures as specified in the Schedule of Assessments ([Table 7.1-1](#)). Subjects will continue treatment with study drug until the subject discontinues study, the study drug becomes clinically available in the subject's locale, or the sponsor terminates the study drug clinical development program.

¹ Reg. US Pat. & Tm. Off.

End of Study (EOS)/ Early Termination (ET) Visit: Subjects will return to the clinic upon conclusion of the study (study drug becomes clinically available in the subject's locale or the sponsor terminates the study drug clinical development program) or early termination for procedures as specified in the Schedule of Assessments ([Table 7.1-1](#)).

Figure 7.1-1: Study Schematic



EOS=end of study; ET=early termination; M=month; V=visit.

*Corresponds to Visit 9 in Protocols 093-045 and 093-046. **1200 mg QD for subjects who had a dose reduction while participating in Protocols 093-045 or 093-046.

Table 7.1-1: Schedule of Assessments

Procedures	Visit 1/ SCN ^a	Visit 2	Visit 3	Visit 4	Visits 5 and 6	Visit 7	Post-1-year Visit 8 onwards	EOS/ET	Computer Systems ^c
	Day 0	Week 1	Month 1	Month 3	Months 6 and 9	Month 12	Month 15 onwards ^b		
Informed Consent	X								
Inclusion/Exclusion Criteria Review	X								A
Physical Examination	• ^d							X	A
Neurological Examination	•							X	A
Vital Sign Measurements	•	X	X	X	X	X	X	X	A
Height	•							X	A
Weight ^e	•	X	X	X	X	X	X	X	A
Clinical Laboratory Evaluation (Serum Chemistry, Hematology, and Urinalysis) ^f	•		X	X	X	X		X ^{g,h}	B
Coagulation Testing (PT/INR, PTT)	•		X	X	X	X		X ^g	B
Thyroid Panel (T ₃ , T ₄ , and TSH)	•		X	X	X	X		X ^g	B
Lipid Panel (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides) ^f	•		X	X	X	X		X ^g	B
Bone Turnover Markers ⁱ	•				X ^j	X		X ^g	B
Serum Pregnancy Test ^k	•		X	X	X	X		X ^g	B
Urine Pregnancy Test ^k							X	X	
Urine Drug Screen (Central Lab)	•								B
12-Lead ECG	•		X	X	X	X		X ^h	C
MADRS	•				X ^j	X	X ^l	X	A
QOLIE-31 ^m	•				X ^j	X	X ^l	X	A
PGI Scale							X	X ⁿ	
C-SSRS ^o	•	X	X	X	X	X	X	X	A
Health Outcomes Assessments	•	X	X	X	X	X	X	X	A
Adverse Events	•	X	X	X	X	X	X	X	A
Concomitant Medications	•	X	X	X	X	X	X	X	A
Dispense Seizure Diary	X	X	X	X	X				
Document Seizures in Seizure Diary		X	X	X	X				A
Seizure Diary Review		X	X	X	X	X		X ^g	
Dispense Study Drug	X	X	X	X	X	X ^p	X		A

Table 7.1-1: Schedule of Assessments

Procedures	Visit 1/ SCN ^a	Visit 2	Visit 3	Visit 4	Visits 5 and 6	Visit 7	Post-1-year Visit 8 onwards	EOS/ET	Computer Systems ^c
	Day 0	Week 1	Month 1	Month 3	Months 6 and 9	Month 12	Month 15 onwards ^b		
Dispense Emergency Medication	X								
Drug Accountability		X	X	X	X	X	X	X	A
Dispense/Review MEC	X	X	X	X	X	X	X	X	

Abbreviations: A=Electronic Data Capture (Inform); B=Laboratory Information Management System (LIMS); C=Core Lab Over-Read; C-SSRS=Columbia Suicidality Severity Rating Scale; EOS=End of Study; ET=Early Termination; MADRS=Montgomery-Asberg Depression Rating Scale; NTx=N-telopeptides of type I collagen cross-links; SCN=Screening; 25-OHD=25-hydroxyvitamin D; TSH=thyroid stimulating hormone; PGI=Patient Global Impression; PTH=parathyroid hormone; QOLIE-31=31-Item Quality of Life in Epilepsy.

- a. Demographic information, medical history, psychiatric history, medication history, magnetic resonance imaging/computerized tomography scans, electroencephalogram data, HLA-B*1502 genotyping, and Hepatitis B/C screen results collected during the screening visit of Protocols 093-045 or 093-046 will apply for this study as well.
- b. Clinic visits to occur at intervals of 3 months during the post-1-year part.
- c. Letters in this column identify the computerized systems that will be used in this protocol ([Appendix IX](#)).
- d. The symbol “•” represents procedures performed at Visit 9 of Protocols 093-045 or 093-046, the results of which will apply to Visit 1 of the present study as well. These procedures do not have to be repeated.
- e. In street clothes without shoes and jacket/coat.
- f. Fasting labs.
- g. These assessments are not required to be performed if this visit falls in the post-1-year part of the study.
- h. If this visit falls in the post-1-year part of the study, this assessment may be performed only if clinically indicated (per Investigator judgment) eg, as a follow-up on a previously noted abnormality.
- i. Includes serum 25-OHD, PTH, osteocalcin, bone-specific alkaline phosphatase, and urinary NTx.
- j. At Visit 5 only.
- k. In female subjects of child bearing potential only.
- l. Every 6 months (ie, Visits 7, 9, 11, 13 etc.).
- m. Only in subjects ≥18 years at time of signing informed consent in Protocols 093-045 or 093-046.
- n. Only for subjects who discontinue study during the post-1-year part of study.
- o. Fill out “since last visit” scale ([Appendix VII](#)).
- p. Only for subjects who continue into the post-1-year part of the study.

7.2. Study Endpoints

7.2.1. 1-Year Safety Endpoints

1. Clinical evaluations (adverse events, vital signs, orthostatic effects, physical and full neurological examination, body weight, and 12-lead ECGs).
2. Clinical laboratory evaluations (serum chemistry, hematology and urinalysis), high-density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol, and triglycerides), coagulation testing (PT/INR, and PTT), bone turnover markers (serum 25-hydroxyvitamin D [25-OHD], parathyroid hormone [PTH], osteocalcin, bone-specific alkaline phosphatase, and urinary N-telopeptides of type I collagen cross-links [NTx]).
3. Proportion (%) of subjects with increase of body weight $\geq 7\%$.
4. Proportion (%) of subjects with normal baseline blood sodium reaching levels of ≤ 135 mmol/L, ≤ 130 mmol/L, and ≤ 125 mmol/L.
5. Columbia Suicidality Severity Rating Scale (C-SSRS).

7.2.2. 1-Year Efficacy Endpoints

1. Time on eslicarbazepine acetate monotherapy.
2. Seizure frequency reduction from baseline period (Visit 1 to 2) of Protocols 093-045 or 093-046.
3. Responder rate (proportion [%] of subjects with a $\geq 50\%$ reduction of seizure frequency from baseline period [Visit 1 to 2] of Protocols 093-045 or 093-046).
4. Proportion (%) of subjects who are seizure-free during 1-year period (determined in 12-week intervals).
5. Seizure frequency by seizure type.
6. Completion rate (proportion [%] of subjects completing the 1-year treatment).
7. Treatment retention time (time to withdrawal due to lack of efficacy or adverse events).
8. Change in total score from Visit 2 (Day 0) of Protocols 093-045 or 093-046 to end of study treatment (Visit 7, Month 12) in 31-Item Quality of Life in Epilepsy (QOLIE-31).
9. Change in total score from Visit 2 (Day 0) of Protocols 093-045 or 093-046 to end of study treatment (Visit 7, Month 12) in Montgomery-Asberg Depression Rating Scale (MADRS).
10. Change in total score from Visit 2 (Day 0) of Protocols 093-045 or 093-046 to end of study treatment (Visit 7, Month 12) in MADRS in those subjects with a MADRS score of ≥ 14 at screening visit of the present study.

7.2.3. Post 1-year Endpoint

1. Fraction of subjects who completed treatment at each visit post-1-year.

7.3. Study Assessments

7.3.1. Safety Assessments

1. 12-Lead ECG, physical and full neurological examinations, and orthostatic effects and vital signs as specified in the Schedule of Assessment (Table 7.1-1).

Note: Not all orthostatic effects qualify as adverse events (AE). The decision to report an orthostatic effect as an AE will be made by the investigator based upon the overall clinical picture of the incident. Orthostatic changes with clinically significant symptoms should be recorded as AEs. See also Sections 13.1.1, Objective Findings and 14.7.8.1, Orthostatic Effects.

2. Clinical laboratory evaluation (serum chemistries, hematology, and urinalysis), thyroid panel (T3, T4, and TSH), lipid panel (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides), and coagulation testing (PT/INR, and PTT) as specified in the Schedule of Assessment (Table 7.1-1). Bone turnover markers (serum 25-OHD, PTH, osteocalcin, bone-specific alkaline phosphatase, and urinary NTx) as specified in the Schedule of Assessment (Table 7.1-1).
3. Body weight as specified in the Schedule of Assessment (Table 7.1-1).
4. Adverse event monitoring as specified in the Schedule of Assessment (Table 7.1-1).
5. C-SSRS¹⁶ will be completed by the Investigator or Sub-Investigator (or qualified site personnel) as specified in the Schedule of Assessment (Table 7.1-1). The C-SSRS is used to determine the presence and severity of suicidality in subjects (Appendix VII).

7.3.2. Efficacy Assessments

Seizure Diary

Each subject will be instructed to keep a seizure diary (Appendix X) and record information on all seizures for the first one-year of the study starting from Visit 1 (Screening) and ending at Visit 7 (see Table 7.1-1). Subjects or caregivers can complete the study diary; however the person who maintains the diary should remain the same throughout the study. Seizure occurrences since the previous visit, based on review of the seizure diary, will be recorded by date and seizure type on the eCRF.

Other Efficacy Assessments

The effect of eslicarbazepine acetate on other aspects of epilepsy will be evaluated by measuring the change from baseline of the following scales as specified in the Schedule of Assessment (Table 7.1-1):

1. The Montgomery-Asberg Depression Rating Scale (MADRS)¹⁷ will be performed by a credentialed and trained MADRS rater (please see Section 11.2, Guidelines for MADRS

Rater). The MADRS measures the severity of a subject's depressive symptoms ([Appendix V](#)).

2. The 31-Item Quality of Life in Epilepsy Scale (QOLIE-31)¹⁸ will be subject self-administered. Subjects will be given sufficient time to complete this questionnaire ([Appendix VI](#)). The QOLIE-31 will be administered only in subjects who have completed 18 years of age at time of signing informed consent in Protocols 093-045 or 093-046.
3. The Patient Global Impression (PGI) scale will be subject self-administered at all visits during the post-1-year period only. The scale measures the patient impression of improvement in disease ([Appendix XIV](#)).

7.3.3. Health Outcomes Assessments

Data on utilization of health care services which are not study protocol driven will be collected. An assessment of health care resource use for seizure-related care will be performed. The assessment will be performed for exploratory purposes to inform future study designs, generate additional study hypotheses, and to provide initial inputs for the development of a health economic predictive model. These data will be collected as specified in the Schedule of Assessments ([Table 7.1-1](#)). The site staff may use the review of subject entries in the Medical Events Calendar (MEC) as a source to determine if further data about the subject's utilization of health care services should be obtained.

Results of the health outcomes analysis will be described in a separate report other than the clinical study report.

8. Selection and Withdrawal of Subjects

8.1. Subject Inclusion/Exclusion Criteria

1. Subject who completed, exited, or discontinued for reasons other than safety from the 18-week treatment phase of Protocols 093-045 or 093-046 and are willing to continue participation in this study are eligible. Subject must have completed at least the first 3 weeks of the 18-week double-blind treatment period of Protocols 093-045 or 093-046 to be eligible.
2. Subject must give written informed consent prior to participation in the study. For subjects <18 years of age, the informed consent must be signed by the subject's parent or legal guardian, and, when appropriate and/or required by state or local law, minor subjects must give written informed assent prior to participation in the study. All subjects must sign privacy authorization form, if applicable. All females of child bearing potential (≤ 65 years of age) must also sign the "Women of Childbearing Potential" Addendum.
3. Subjects must, in the opinion of the Investigator (with consultation with Medical Monitor as appropriate), continue to potentially benefit from continued study participation and have no new medical conditions that would preclude study participation.
4. If female subject, must continue the accepted method of birth control defined in Protocols 093-045 or 093-046 for the duration of this study as well.

8.2. Subject Withdrawal/Discontinuation Criteria

1. Subject with serum sodium level ≤ 125 mmol/L.
2. Subject with any kind of hypersensitivity (especially manifested as rash) suspected to be induced by eslicarbazepine, carbamazepine, oxcarbazepine, or chemically-related substances.
3. Subject who needs to initiate prohibited concomitant medications.
4. Subject who needs to reduce eslicarbazepine acetate dose to <800 mg QD or increase dose to >2400 mg QD.
5. Subject who needs to use >2 additional AEDs. If applicable, provide sufficient study drug to taper subject off of study drug (taper schedule is at the Investigator's discretion). Schedule a follow-up (unscheduled) visit, if applicable, to assess AEs and to collect all remaining study drug in the original container (including any empty containers).

Please also refer to [Section 12](#), Discontinuation and Replacement of Subjects.

8.2.1. Criterion for Continuation into the Post-1-year Part of Study

For subjects to continue into the post-1-year part of the study, subjects must, in the opinion of the Investigator (with consultation with Medical Monitor, appropriate), continue to potentially benefit from continued study participation and have no new medical conditions that would preclude study participation.

9. TREATMENT OF SUBJECTS

9.1. Concomitant Medications

9.1.1. Disallowed Medications

The following medications are not allowed in the study:

- Oxcarbazepine
- The following CNS medications are not allowed:
 - Antipsychotics;
 - Tricyclic antidepressants;
 - Anxiolytics (including benzodiazepines with exception of rescue and emergency medication as listed in Appendices XII and XIII);
 - Sedative hypnotics including non-benzodiazepines (see exceptions below, Section 9.1.2);
 - Central opioid agonists/antagonists;
 - Monoamine oxidase inhibitors (MAOIs);
 - Marijuana;
 - Initiation of any treatment with amphetamines.

9.1.2. Concomitant Medications Allowed for the Duration of the Study

- Stable use of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).
 - Trazodone is allowed during study.
- Occasional use of rescue medication (no more than once every 28 days) as described in [Appendix XII](#).
- Occasional use of lorazepam or other benzodiazepine as sleeping medication (no more than once every 28 days).
- Occasional use of newer generation non-benzodiazepine sleep medications (zolpidem, eszopiclone, ramelteon, or zaleplon) (maximum of once per week).
- Occasional use of OTC sleep medications (eg, diphenhydramine, melatonin, or herbal preparation) (maximum of twice per week).
- Emergency medication (as described in [Appendix XIII](#)).
- Concomitant medications (eg, drugs like theophylline, coumadin, etc.) whose plasma dose levels may significantly change after withdrawal or addition of enzyme inducing

AEDs (such as carbamazepine or phenytoin) during the study should be properly monitored and their dose adjusted as indicated.

Hormonal contraceptives are allowed if the subject is on a stable dose for at least 30 days prior to Visit 1 and agrees to continue such use throughout the duration of the study and for 30 days after the final dose of study drug. All females on oral contraceptives and hormonal therapy should be encouraged to dose at the same time of day each day while on study.

Chronic medications taken concomitantly during the preceding double-blind study are allowed (dose adjustments may be made as needed). Other treatments may be initiated as medically needed except with medications listed in [Section 9.1.1](#) in which case the subject should be discontinued from the study.

Administration of eslicarbazepine acetate 1200 mg QD to female subjects in a previous clinical study showed a decrease in systemic exposure to both hormones of a combined oral contraceptive containing levonorgestrel and ethinyloestradiol, most likely caused by an induction of CYP3A4 in vivo. Therefore, it must be taken into account that concomitant use of eslicarbazepine acetate and hormonal contraceptives may render these contraceptives ineffective.

Subjects using implanted, injectable, or hormonal contraceptives therefore, must use additional methods of contraception for the duration of the study.

9.2. Treatment Compliance

Each subject's treatment compliance with administration of study drug will be assessed by interview and counting the number of returned study drug tablets. Subjects will be instructed to return all unused study drug and empty packaging at each visit.

9.3. Randomization and Blinding

Not applicable.

9.4. Unblinding Procedures

Not applicable.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Description of Study Drug

The study drug will be provided as 400 mg tablets of eslicarbazepine acetate [(S)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide]. Subjects will be instructed to take tablets at the same time once daily in the morning.

10.2. Study Drug Packaging and Labeling

Subjects will be dispensed multiple 100-count HDPE (plastic) tamper-evident sealed bottles containing 100 tablets each per assigned dosing. All packaging for study drug will be labeled with:

- Protocol number
- Sponsor's name and address
- Local Country Caution Statement
- Instructions for use and storage
- Container number(s) to be entered into the eCRF
- Blank space for Site No.
- Blank Space for Subject No.
- Blank Space for Visit No.
- Blank Space for Investigator name
- EudraCT Number
- Lot/Batch Number
- Expiry
- Storage Conditions

10.3. Study Drug Storage

Eslicarbazepine acetate should be kept out of the reach and sight of children. It should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).

10.4. Study Drug Preparation

Not applicable.

10.5. Study Drug Administration

Study drug will be supplied as 400 mg tablets of eslicarbazepine acetate. Subjects will be required to take their study drug once every day in the morning with water, with or without food, at approximately the same time every day.

- Subjects receiving 800 mg eslicarbazepine acetate per day will take two 400 mg tablets per day.
- Subjects receiving 1200 mg eslicarbazepine acetate per day will take three 400 mg tablets per day.
- Subjects receiving 1600 mg eslicarbazepine acetate per day will take four 400 mg tablets per day.
- Subjects receiving 2000 mg eslicarbazepine acetate per day will take five 400 mg tablets per day.
- Subjects receiving 2400 mg eslicarbazepine acetate per day will take six 400 mg tablets per day.

All tablets are to be taken simultaneously, when applicable.

In countries where available, subjects will be provided with lorazepam (2 mg sublingual) for rescue use and diazepam rectal gel (2.5 mg, 2-pack diazepam; Diastat[®]) for emergency medication use. In countries where lorazepam and/or diazepam rectal gel are not available please refer to [Appendices XII](#) and [XIII](#) for alternate treatments for rescue and emergency use.

10.6. Study Drug Accountability

The Investigator is responsible for storing the study drug in a secure location and for maintaining adequate records of drug disposition that includes the dates, quantity, and use by subjects. If the study is terminated, discontinued, suspended, or completed, all unused supplies of study drug will be returned to Sunovion Pharmaceuticals Inc. or designee, unless other instructions are provided in writing by Contract Research Organization (CRO)/Sponsor. A drug inventory record will be supplied. The Investigator on an ongoing basis must maintain a drug inventory record of supplied, received, dispensed, and returned medication.

The study drug will not be dispensed to any person who is not a study subject under this protocol.

10.7. Study Drug Handling and Disposal

The Investigator is required to return all unused study drug to the Sponsor or designee as instructed. The Investigator is required to maintain copies of medication shipping receipts, drug accountability records, and records of return or final disposal of study drug.

11. TREATMENT PLAN

11.1. Standardization of Data Capture

Study Schematic (Figure 7.1-1) and Schedule of Assessments (Table 7.1-1): [Figure 7.1-1](#) and [Table 7.1-1](#) provide a summary of the study design and the procedures to be conducted at each visit.

Clinic Visits: Clinic visits should be scheduled in the morning when subjects are required to come in a fasting state.

Assessment Windows: Assessments will be conducted as specified in Section 11, Treatment Plan. Vital signs and ECGs should be collected prior to blood draws. All times are relative to the time when individual subjects arrive for their clinic visit.

Vital Signs: Vital signs will be collected at all clinical visits. For each visit, vital signs following ≥ 5 minutes rest, consisting of supine systolic and diastolic blood pressures, respiration rate, heart rate, and oral body temperature will be measured. Blood pressure (BP) and heart rate (HR) should first be taken with the subject in the supine position after resting for ≥ 5 minutes. Blood pressure and heart 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 heart 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 heart rate should be collected at that time in the manner described above. Vital signs will be obtained after ECG and prior to clinical laboratory collection. Subject's respiration rate and body temperature will also be collected as part of vital sign measurement. Height will be measured at Visits 1 and EOS/ET visit only. Weight will be measured at all clinical visits.

Electrocardiograms: ECGs will be performed as outlined in the Schedule of Assessments, [Table 7.1-1](#). The post-1-year EOS/ET visit ECG is to be collected only if clinically indicated (as judged by the Investigator) eg, as follow-up on a previously noted abnormality. . 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 vital sign measurements and drawing blood samples. All ECGs (except for the post-1-year EOS/ET ECG, if performed) will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability. See [Appendix III](#), Cardiac Safety Monitoring/ECG for collection guidelines.

Clinical Laboratory Evaluation: All clinical laboratory evaluations required by the protocol are outlined in [Appendix II](#) (Clinical Laboratory Tests). All clinical laboratory evaluations are to be collected in the fasting state. For detailed instructions regarding laboratory procedures, sampling, and shipping guidelines refer to the Central Laboratory Instructions Manual. Blood samples will be collected at as outlined in the Schedule of Assessments, [Table 7.1-1](#) and processed at a central laboratory to ensure consistency. All laboratories will be College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

Seizure Diary: All subjects will be given a seizure diary ([Appendix X](#)) at Visits 1 through 6 to be completed throughout their time on study. Subjects or caregivers can complete the seizure diary; however the person who maintains the diary should remain the same throughout the study. Subjects will record information on their seizures in the seizure diary by date and type. At each return visit (Visits 2 through 6), the seizure diary will be reviewed, collected, and a new seizure diary will be dispensed. At Visit 7, the seizure diary will be reviewed and collected only. A new one will not be dispensed.

Medical Events Calendar: All subjects will be given a medical events calendar (MEC, [Appendix VIII](#)) as specified in the Schedule of Assessment ([Table 7.1-1](#)) to be completed throughout their time on study. Subjects will record changes in health status or medications in the MEC. At each return visit, the MEC will be reviewed, collected, and a new MEC will be dispensed. At the EOS/ET visit, the MEC will be reviewed and collected only.

Adverse Events: Using the MEC as a discussion guide, 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?”).

Concomitant Medications: Subject self-report will be acceptable for listing all concomitant medication use and evaluation for inclusion/exclusion (Visit 1) except where specific protocol procedures are mandated to ensure appropriate enrollment (eg, certain baseline lab values).

Rating Scales: The MADRS will be administered by a credentialed and trained MADRS rater (see [Section 11.2](#)) as specified in the Schedule of Assessments ([Table 7.1-1](#)) ([Appendix V](#)). The rater shall be asked to avoid inquiring about or evaluating AEs. The C-SSRS will be administered by a trained Investigator or Sub-Investigator (or qualified site personnel) as specified in the Schedule of Assessments ([Table 7.1-1](#)) ([Appendix VII](#)). The QOLIE-31 is subject self-administered and will be administered as specified in the Schedule of Assessments ([Table 7.1-1](#)) ([Appendix VI](#)). The PGI scale will be subject self-administered during all visits in the post-1-year part of the study.

11.2. Guidelines for MADRS Rater

The MADRS must be administered via the Structured Interview Guide for the MADRS (SIGMA) by a credentialed and trained MADRS rater who is a qualified clinician. The scoring must be based upon symptom severity assessed/personally observed by the MADRS rater at the time of the structured interview. Assessments must be based entirely upon information gained from the interview without any input from third parties or other efficacy or safety assessments. Furthermore, interviews by the MADRS rater must be limited to discussion of depression-related symptoms measured by this scale and absolutely must avoid discussion of ancillary topics (eg, AEs).

The SIGMA was developed to standardize the manner of administration of the MADRS scale. Ratings should be based on the subject’s condition over the prior 7 days.

At all post-baseline interviews, assessments must be made entirely upon information gained at the interview with the subject without reference to other test results.

11.3. Electronic Data Capture

The study sites will use a validated electronic data capture (EDC) system to enter subject data onto electronic case report forms (eCRFs). The Inform EDC system through Quintiles will be used for this clinical study. Password protected access to the EDC system will be via a secure website. Data clarification forms and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed electronic case report forms must be reviewed and electronically signed and dated by the Investigator. In compliance with remote data retention requirements, the study sites will be provided with a CD-ROM containing the eCRFs and the complete audit trail in PDF format, subsequent to database lock.

11.4. Study Visits

Subjects should be instructed to fast overnight (minimum 8 hours) before each scheduled in-clinic visit for which blood samples are to be collected.

11.4.1. Screening: Visit 1 (Day 0)

Subjects will be evaluated at the Screening Visit to determine their eligibility to enroll in the study. **Visit 1 of this study corresponds to Visit 9 of Protocols 093-045 and 093-046. The following procedures are also performed at Visit 9 of Protocols 093-045 and 093-046 and therefore do not have to be duplicated in the present study.** The results of the following Visit 9 procedures will apply to this study as well.

- Obtain information on adverse events (AEs) and concomitant medication.
- Administer the MADRS, QOLIE-31, and C-SSRS.
- Perform Health Outcomes assessments based upon entries in the MEC and discussion with the subject during the visit.
- Perform a physical examination, including a full neurological examination.
- Perform a standard 12-lead ECG with 10-second rhythm strip.
- Obtain vital signs including height and weight.
- Obtain blood and urine samples for clinical laboratory evaluation (serum chemistry, hematology, and urinalysis), coagulation testing, thyroid panel, lipid panel, bone turnover markers, serum pregnancy test (female subjects of child bearing potential only), and urine drug screen (central lab).
- Issue the seizure diary and instruct subject on its use.
- Issue MEC and instruct the subject on its use.

The following procedures are specific to the present study and are to be performed at Screening:

- Obtain signed informed consent (including women of child-bearing potential addendum, if applicable) and privacy authorization from the subject before conducting any other visit procedures. Obtain informed assent for subjects <18 years and signed informed consent from the parent or legal guardian.
- Assess inclusion/exclusion criteria.
- Dispense study drug.
- Schedule Visit 2 to occur in 1 week and instruct the subject to bring the seizure diary and the MEC to Visit 2. Remind subject to come to next scheduled clinic visit (Visit 2) in a fasting state.

The PI or designee must confirm the subject has a valid prescription for rescue and emergency medication or that medication is still available from participation in the double-blind study (Protocol 093-045 or 093-046), as applicable (see [Appendices XII](#) and [XIII](#)) at the screening visit so that the subject will have the medication at Visit 2. For sites in the United States, the PI may fax the prescription to the central pharmacy at least 10 days before the expected screening visit. For sites in Canada, the prescription should be provided to the subject and the subject asked to fill the prescription before returning to the site for Visit 2.

11.4.2. Visit 2 (Week 1±1 day)

The following study-related procedures will be performed at Visit 2.

- Collect and review the seizure diary and MEC. Record changes in concomitant medications, including over-the-counter (OTC) and health and dietary supplements, and AEs that may have occurred between Visit 1 and Visit 2.
- Administer the C-SSRS scale.
- Perform Health Outcomes assessments based upon entries in the MEC and discussion with the subject during the visit.
- Obtain vital signs including weight.
- Dispense study drug.
- Perform drug accountability.
- Re-dispense the seizure diary and MEC.
- Schedule Visit 3 to occur after 3 weeks of Visit 2. Remind subject to bring all remaining Visit 2 study drug in the original container (including any empty containers), seizure diary, and the MEC to the next scheduled visit. Remind subject to come to next scheduled visit in a fasting state.

11.4.3. Visit 3 (Month 1±3 days)

The following assessments will be conducted at the Month 1 visit (Visit 3):

- Collect and review the seizure diary and MEC. Record changes in concomitant medications, including OTC and health and dietary supplements, and AEs that may have occurred between Visit 2 and Visit 3.
- Administer the C-SSRS scale.
- Perform Health Outcomes assessments based upon entries in the MEC and discussion with the subject during the visit.
- Perform a standard 12-lead ECG with 10-second rhythm strip.
- Obtain vital signs including weight.
- Obtain blood samples for clinical laboratory evaluation (serum chemistry, hematology, and urinalysis), coagulation testing, thyroid panel, lipid panel, and serum pregnancy test (female subjects of child bearing potential only).
- Dispense study drug.
- Perform drug accountability.
- Re-dispense the seizure diary and MEC.
- Schedule Visit 4 to occur within 2 months after Visit 3. Remind subject to bring all remaining Visit 3 study drug in the original container (including any empty containers), seizure diary, and the MEC to the next scheduled visit. Remind subject to come to next scheduled clinic visit in a fasting state.

11.4.4. Visit 4 (Month 3±1 week)

The following assessments will be conducted at the Month 3 visit (Visit 4):

- Collect and review the seizure diary and MEC. Record changes in concomitant medications, including OTC and health and dietary supplements, and AEs that may have occurred between Visit 3 and Visit 4.
- Administer the C-SSRS scale.
- Perform Health Outcomes assessments based upon entries in the MEC and discussion with the subject during the visit.
- Perform a standard 12-lead ECG with 10-second rhythm strip.
- Obtain vital signs including weight.
- Obtain blood samples for clinical laboratory evaluation (serum chemistry, hematology, and urinalysis), coagulation testing, thyroid panel, lipid panel, and serum pregnancy test (female subjects of child bearing potential only).
- Dispense study drug.
- Perform drug accountability.
- Re-dispense the seizure diary and MEC.

- Schedule Visit 5 to occur within 3 months after Visit 4. Remind subject to bring all remaining Visit 4 study drug in the original container (including any empty containers), seizure diary, and the MEC to the next scheduled visit. Remind subject to come to next scheduled clinic visit in a fasting state.

11.4.5. Visit 5 (Month 6±1 week)

The following assessments will be conducted at the Month 6 visit (Visit 5):

- Collect and review the seizure diary and MEC. Record changes in concomitant medications, including OTC and health and dietary supplements, and AEs that may have occurred between Visit 4 and Visit 5.
- Administer the MADRS, QOLIE-31, and C-SSRS scales.
- Perform Health Outcomes assessments based upon entries in the MEC and discussion with the subject during the visit.
- Perform a standard 12-lead ECG with 10-second rhythm strip.
- Obtain vital signs including weight.
- Obtain blood samples for clinical laboratory evaluation (serum chemistry, hematology, and urinalysis), coagulation testing, thyroid panel, lipid panel, bone turnover markers, and serum pregnancy test (female subjects of child bearing potential only).
- Dispense study drug.
- Perform drug accountability.
- Re-dispense the seizure diary and MEC.
- Schedule Visit 6 to occur 3 months after Visit 5. Remind subject to bring all remaining Visit 5 study drug in the original container (including any empty containers), seizure diary, and the MEC to the next scheduled visit. Remind subject to come to next scheduled clinic visit in a fasting state.

11.4.6. Visit 6 (Month 9±1 week)

The following assessments will be conducted at the Month 9 visit (Visit 6):

- Collect and review the seizure diary and MEC. Record changes in concomitant medications, including OTC and health and dietary supplements, and AEs that may have occurred between Visit 5 and Visit 6.
- Administer the C-SSRS scale.
- Perform Health Outcomes assessments based upon entries in the MEC and discussion with the subject during the visit.
- Perform a standard 12-lead ECG with 10-second rhythm strip.

- Obtain vital signs including weight.
- Obtain blood samples for clinical laboratory evaluation (serum chemistry, hematology, and urinalysis), coagulation testing, thyroid panel, lipid panel, and serum pregnancy test (female subjects of child bearing potential only).
- Dispense study drug.
- Perform drug accountability.
- Re-dispense the seizure diary and MEC.
- Schedule Visit 7 to occur within 3 months after Visit 6. Remind subject to bring all remaining Visit 6 study drug in the original container (including any empty containers), seizure diary, and the MEC to the next scheduled visit. Remind subject to come to next scheduled visit in a fasting state.

11.4.7. Visit 7 (Month 12±1 week)

The following assessments will be conducted at the Month 12 visit (Visit 7):

- Collect and review the seizure diary and MEC. Record changes in concomitant medications, including OTC and health and dietary supplements, and AEs that may have occurred between visit 6 and Visit 7.
- Administer the MADRS, QOLIE-31, and C-SSRS scales.
- Perform Health Outcomes assessments based upon entries in the MEC and discussion with the subject during the visit.
- Perform a standard 12-lead ECG with 10-second rhythm strip.
- Obtain vital signs including weight.
- Obtain blood samples for clinical laboratory evaluation (serum chemistry, hematology, and urinalysis), coagulation testing, thyroid panel, lipid panel, bone turnover markers, and serum pregnancy test (female subjects of child bearing potential only).
- Perform drug accountability.
- Ask subject to choose if wants to continue receiving study drug and continue into the post-1-year part of the study.
 - Subjects who choose not to continue into the post-1-year part of the study, this visit is considered as the EOS visit and additional procedures (eg, physical examination, neurological examination, urine pregnancy test [female subjects of child bearing potential only], and height) as specified in [Section 11.4.9](#) are to be followed.
 - If subject continues into the post-1-year part of the study:
 1. Schedule Visit 8 to occur within 3 months after Visit 7.
 2. Dispense study drug and MEC.

3. Remind subject to bring all remaining Visit 7 study drug in the original container (including any empty containers), and the MEC to the next scheduled visit.

11.4.8. Post-1-year Visit 8 and all Visits onwards (Month 15 and onwards until EOS or ET)

Subjects who choose to continue into the post-1-year part of the study will visit the clinic at 3-month intervals until EOS or ET (see [Section 11.4.9](#)). At each post-1-year visit, the following assessments will be conducted:

- Collect and review the MEC. Record changes in concomitant medications, including OTC and health and dietary supplements, and AEs that may have occurred between this visit and the last clinical visit.
- Administer the C-SSRS scale.
- Administer the MADRS and QOLIE-31 scales (only at alternate visits [coinciding with 6-month intervals from Visit 7 ie, Visits 7, 9, 11, 13 etc]).
- Administer the PGI scale.
- Perform Health Outcomes assessments based upon entries in the MEC and discussion with the subject during the visit.
- Obtain vital signs including weight.
- Obtain urine sample for urine pregnancy test (female subjects of child bearing potential only).
- Dispense study drug.
- Perform drug accountability.
- Re-dispense the MEC.
- Schedule the next visit to occur within 3 months of this visit. Remind subject to bring all remaining previous visit study drug in the original container (including any empty containers), and the MEC to the next scheduled visit.

11.4.9. End of Study/Early Termination

The following assessments will be conducted for the EOS/ET Visit:

- Collect and review the seizure diary (for subjects who discontinue in the 1-year part of study only) and MEC. Record changes in concomitant medications, including OTC and health and dietary supplements, and AEs that may have occurred since last visit.
- Administer the MADRS, QOLIE-31, and C-SSRS scales.
- Administer the PGI scale (only for subjects who continued in to the post-1-year period of the study).

- Perform Health Outcomes assessments based upon entries in the MEC and discussion with the subject during the visit.
- Perform a physical examination, including a full neurological examination.
- Perform a standard 12-lead ECG with 10-second rhythm strip (for subjects who discontinue in the post-1-year part of study, this assessment is to be performed only if clinically indicated [per Investigator judgement] eg, as follow-up on a previously noted abnormality. A post-1-year ECG assessment, if performed, is not to be overread).
- Obtain vital signs including weight and height.
- Obtain blood samples for clinical laboratory evaluation (serum chemistry, hematology, and urinalysis), coagulation testing, thyroid panel, lipid panel, bone turnover markers, and serum and urine pregnancy test (female subjects of child bearing potential only). For subjects who discontinue in the post-1-year part of study, only the urine pregnancy test (in female subjects of child bearing potential only) is to be performed. Serum chemistry, hematology, and urinalysis to be performed only if clinically indicated (per Investigator judgement) eg, as follow-up on a previously noted abnormality.
- Perform drug accountability.
- Ask subject to initiate other AEDs (if applicable).
- If applicable for early termination or discontinued subjects, provide sufficient study drug to taper the subject off of study drug as needed (taper schedule is at the Investigator's discretion).
- If applicable, schedule a follow-up (unscheduled) visit to assess AEs and to collect all remaining study drug in the original container (including any empty containers).

12. DISCONTINUATION AND REPLACEMENT OF SUBJECTS

Subjects in this clinical study may be discontinued for any of the following reasons:

- Adverse event
- Protocol violation
- Withdrawal of consent
- Lost to follow-up
- Physician decision
- Other

Every effort should be made for all subjects prematurely discontinuing from the study, regardless of cause, to undergo final evaluation procedures, in accordance with [Section 11.4.9](#), Early Termination Visit.

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 that is not consistent with protocol participation, (eg, violates inclusion/exclusion criteria), the subject must be discontinued.

Subjects whose study participation is prematurely terminated will not be replaced.

Please also see [Section 8.2](#), Subject Withdrawal/Discontinuation Criteria.

13. ADVERSE EXPERIENCE REPORTING

13.1. Adverse Events

An AE is any reaction, side effect or other undesirable event that occurs in conjunction with the use of the study drug, whether or not the event is considered drug-related.

Adverse events will be collected from the time the informed consent is signed to the end of the study. Serious adverse events (SAEs) will be collected and reported on the SAE form, from the time of informed consent to 30 days post–last-dose and will be followed until resolution or lost to follow-up. SAEs occurring from the time of informed consent to the end of study must be recorded on the eCRF and the data recorded should match that on the SAE form.

Non-leading questions will be used to ask subjects about the possible occurrence of 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.

Following questioning and evaluation, all AEs, whether believed by the Investigator to be related or unrelated to the study drug, must be documented in the subject’s study records/source documents, in accordance with the Investigator’s normal clinical practice, and on the AE page of the eCRF. Each AE is to be evaluated for duration, intensity, seriousness, and causal relationship to the study drug. [Appendix IV](#) (Definitions for Reporting Adverse Events) provides definitions for severity of an adverse event, relationship to study drug, frequency, and action taken. An AE is deemed associated with the use of the study drug “if there is a reasonable possibility that the experience may have been caused by the drug” (21 CFR 312.32 [a]).

The Medical Monitor is the initial contact person for protocol-related questions or discussion of adverse events. The name and contact information of the Medical Monitor is provided on page 3 of this protocol.

13.1.1. Objective Findings

New and worsening signs and symptoms of underlying or emerging disease must be recorded as adverse events. Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded on the Adverse Event page of the eCRF. 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 adverse event.

Clinical laboratory test results will be reviewed by an Investigator as they become available. The Investigator must determine the clinical significance of all out of range values and assign a deviation code. 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. Laboratory reports will be initialed and dated on all pages by a 1572-listed Investigator.

Abnormal laboratory findings will be rated according to the following scale:

- 1 = Deviation from reference range and not clinically significant; not related to underlying condition or disease;
- 2 = Deviation from reference range and not clinically significant; related to any underlying condition or disease; or
- 3 = Deviation from reference range and clinically significant (to be followed until normalized or new baseline; if post-screening, a corresponding AE must be recorded).

A positive drug screen does not require a deviation code.

13.1.2. Immediately Reportable Events

There are two categories of medical events that could occur during participation in a clinical study that must be immediately reported to PPD Pharmacovigilance (PVG):

- Serious adverse event (SAE), including death
- The incidence of pregnancy

PPD PVG must be contacted immediately upon first knowledge of the incident.

PPD PVG:

Hotline Number: (919) 456-6001

Fax: (919) 654-0211

Email: SunovionSafety@druginfo.com

Emergency contact information is also provided on page 3 of this protocol.

A SAE is any untoward medical occurrence at any dose that results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. In addition, based on medical and scientific judgment, important medical events that do not result in any of the outcomes listed above but may jeopardize the subject or require medical or surgical intervention to prevent one of these outcomes, should also usually be considered serious.

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.

If an Investigator or study site staff becomes aware of a serious adverse experience that occurs in a study subject from the time that informed consent is signed through 30 days following the last dose of study drug, this must be reported immediately to PPD PVG.

In addition to the initial telephone notification, an initial SAE form as applicable must be completed and sent via fax to PPD PVG within 1 business day of an Investigator or study site staff becoming aware of the event. Sunovion Pharmaceuticals Inc. provides the SAE form used

to report SAEs as a part of the document package necessary to conduct this clinical study. PPD PVG will forward all SAE reports to Sunovion Pharmaceuticals Inc.

Sunovion Pharmaceuticals Inc. will promptly notify all research sites of an adverse experience that is determined to be reportable to the Regulatory Authorities. These adverse events must be promptly reported to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the Principal Investigator.

If a subject becomes pregnant during the course of the study, she will be instructed to immediately stop taking study drug. Further, the subject will be instructed to return within 48 hours of the first notification of pregnancy to the research site and undergo a serum pregnancy test, as confirmation of pregnancy. If positive, the subject will be immediately discontinued from the study and undergo all early study termination procedures. All pregnancies, whether or not the subject received any study drug, 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 facsimile to PPD PVG within 1 business day of first knowledge by the research personnel of the pregnancy. Sunovion Pharmaceuticals Inc. provides the Pregnancy Event Form as a part of the document package necessary to conduct this clinical study. Pregnancies occurring from the time the informed consent is signed through 30 days following the last dose of study drug will be followed quarterly until birth or termination of the pregnancy.

14. STATISTICS

14.1. General Design

The present study is a 1-year and beyond, multicenter, open-label, flexible dosing safety extension study in male and female subjects (aged 16 to 70 years, inclusive) with partial onset seizures who have just completed, discontinued, or exited the 18-week treatment phase of Protocols 093-045 or 093-046. The study will evaluate the safety and maintenance of effect of long-term eslicarbazepine acetate monotherapy treatment at flexible doses in the range of 800 mg to 2400 mg per day.

Subjects who exit Protocols 093-045 or 093-046 by meeting any of the protocol-defined exit criteria are eligible to participate in this study. Subjects who discontinue from Protocols 093-045 or 093-046 for reasons other than reaching exit criteria may be eligible if there is no safety concern. Subjects must have completed at least the first 3 weeks of the 18-week double-blind treatment period of these studies. Subjects must enter the present study immediately upon completion, discontinuation, or exit from Protocols 093-045 or 093-046.

Subjects who enter the present study will receive a starting dose of 1600 mg QD of eslicarbazepine acetate, orally for a period of 1 week. **The starting dose for subjects who had a dose reduction during participation in studies 093-045 or 093-046 will be 1200 mg and not 1600 mg.** At the end of this 1-week period, subjects will be allowed to continue at this dose or at the discretion of the Investigator, increase, or decrease dose as necessary for efficacy or tolerability reasons. There is no limit on the number of dose increments or reductions during the study, however, all dose increases or reductions should occur in steps of 400 mg and a minimum of 1 week must pass between one dose change and the next. Dose reductions of more than 400 mg are allowed at the discretion of the Investigator for a documented safety reason. The maximum allowed dose of eslicarbazepine acetate is 2400 mg QD and the minimum allowed dose is 800 mg QD in this study.

Subjects with a clinically significant worsening or increase in seizure frequency, who have not responded or did not tolerate an increase in dose of study drug, may be started, at the discretion of the investigator on an additional AED. A maximum of two additional AEDs (excluding oxcarbazepine) to control seizures will be allowed. If, after the addition of the second AED, the subject experiences an adverse event, the dose of eslicarbazepine acetate should be reduced before changing the dose of the concomitant AED. In addition, for subjects with a VNS, the device setting may be changed as needed.

Subjects who require doses outside of the 800 mg QD to 2400 mg QD range or more than 2 other AEDs will be discontinued from study participation.

14.2. Study Endpoints

The study endpoints are listed in [Section 7](#), Investigational Plan.

14.3. Safety Assessments

Safety assessments are described in [Section 7.3.1](#), Safety Assessments.

14.4. Efficacy Assessments

Efficacy assessments are described in [Section 7.3.2](#), Efficacy Assessments.

14.5. Sample Size Determination

Subjects will continue on to this study from Protocols 093-045 or 093-046 as of their own choosing. Therefore, the sample size is outside of statistical considerations.

14.6. Analysis Populations

The intent-to-treat (ITT) population will consist of all subjects who have taken any open-label study medication. The ITT population will be used for safety and efficacy analyses.

14.7. Data Analysis

This section specifies data analysis for the first 1-year study period. Safety and efficacy data collected post-1-year period will be summarized descriptively.

14.7.1. Subject Disposition and Drug Exposure

Subject disposition will be summarized and presented for the number and percentage of subjects, who were enrolled, received open-label treatment, completed the study, and discontinued early (including reasons for discontinuations). Percent compliance will be summarized for the open-label treatment period. The number of tablets taken will be derived as the number of tablets dispensed minus the sum of the number of tablets returned and the number of tablets reported lost. Percent compliance will be derived as the number of tablets taken divided by the number of doses that should have been taken, expressed as a percent. A listing of drug accountability will be presented for all medication distributed to each subject, including number of tablets dispensed, returned, lost/stolen, taken, and overall percent compliance.

The extent of exposure to the open-label medications as well as the number of doses taken will be summarized with descriptive statistics and presented. For each subject, the number of doses taken will be computed from the study drug dispensation and accountability eCRF records obtained at each visit. 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 for the entire open-label period.

14.7.2. Important Protocol Deviations

Prior to database lock, important protocol deviations (IPDs) will be identified in a review of all protocol deviations reported. Possible IPDs will include, but may not be limited to, subjects who:

- Did not meet inclusion/exclusion criteria or eligibility was not adequately verified
- Received any disallowed concomitant medication during open-label treatment period
- Developed withdrawal criteria but were not withdrawn

The potentially important protocol deviations will be identified shortly before database lock, either programmatically (eg, inclusion/exclusion criteria violations) or through review of data listings (eg, investigator comments, concomitant medications). Appropriate personnel (including, at a minimum, a medical director, and a biostatistician) will review the list of potential IPDs to identify which will be considered IPDs. The final list of IPDs will be documented and used to generate a data listing. The number and percentage of subjects with IPDs will be summarized by the categories above.

14.7.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, gender, race (where applicable), height, weight, and BMI, as well as disease conditions, will be summarized using descriptive statistics.

14.7.4. Safety Analysis

Safety outcomes will be analyzed descriptively. Safety variables will include adverse events, vital sign measurements, orthostatic effects, clinical laboratory evaluations (serum chemistry, hematology, and urinalysis), thyroid function, lipid levels, coagulation testing, and bone turnover markers, body weight, blood sodium levels, ECG readings, and C-SSRS.

14.7.5. Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 11.0 or higher. Treatment-emergent adverse events (TEAEs) will be defined as:

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

TEAEs will be summarized by MedDRA system organ class (SOC) and Preferred Term (PT) for the entire study period, as well as for monotherapy period. The monotherapy period includes time since first monotherapy dose to the time when additional AEDs were added, without regard to changes in monotherapy dosage.

The following TEAEs will be summarized and presented by MedDRA SOC and PT:

- All AEs (including number of events and subject incidence)
- AEs by severity (mild, moderate, severe)
- AEs by relationship to treatment (unrelated, or potentially 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 preferred term.
- If a subject reports more than one adverse event within a preferred term and/or a body system, the adverse event with the highest known severity within each body system and within each preferred term will be included in the summaries by severity.
- For summaries by relationship to study drug, AEs whose relationship to treatment is assessed as “not related” will be grouped as “unrelated.” Adverse events assessed as “unlikely,” “possible,” “probable,” or “definite,” unknown or missing will be grouped as “potentially related.” If a subject reports more than one AE within the same treatment regimen, SOC and PT, and any are related, it will be summarized as related.

A listing of serious AEs, as well as a listing of AEs leading to discontinuation or death, will be presented as appropriate.

14.7.6. 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 (PCS) 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. Changes from baseline will be calculated from 093-045 or 093-046 baseline data (Visit 2, Day 0).

14.7.6.1. Blood Sodium Levels

In addition to descriptive summaries of blood sodium levels and changes from baseline for each assessment timepoint, the percent of subjects with normal baseline sodium level reaching ≤ 135 mmol/L but >130 mmol/L, ≤ 130 mmol/L but >125 mmol/L, and ≤ 125 mmol/L will be summarized by timepoint and overall postdose.

14.7.7. Electrocardiograms

ECG parameters and changes in these parameters from baseline will be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and

maximum) at each time point. Changes from baseline will be calculated from 093-045 or 093-046 baseline data.

The number and percentage of subjects with QTc-F values in the following categories will be summarized:

- QTc-F >500 ms at any postdose time point not present at baseline
- QTc-F >450 ms at any postdose time point not present at baseline
- Change from baseline in QTc-F \geq 60 ms for at least 1 postdose measurement
- Change from baseline in QTc-F \geq 30 ms for at least 1 postdose measurement, but <60 ms for all postdose measurements

This categorical analysis will be also performed for QTc-B. The number and percentage of subjects with ECG abnormalities will be presented in the categories of overall, rhythm, conduction, morphology, myocardial infarction and the presence of ST, T, and U wave abnormalities.

14.7.8. Vital Signs

Vital signs, including systolic and diastolic blood pressure, heart rate, weight, and respiratory rate, will be summarized using descriptive statistics at baseline and post open-label treatment visits. Change from baseline (in 093-045 or 093-046) will be included in this presentation as well. In addition, a subject incidence (and percentage) of potentially clinically significant (PCS) vital signs values will be presented. Height at baseline and end of study will be summarized.

14.7.8.1. Orthostatic Effects

Heart rate and both supine and standing blood pressure will be collected as part of the vital signs assessment. Orthostatic effects will be evaluated by summarizing the number and percentage of subjects with a decrease of \geq 20 mmHg in standing systolic or \geq 10 mmHg in standing diastolic blood pressure, as compared to the supine position. The number and percentage of subjects with a heart rate increase of at least 20 beats per minute and heart rate >100 beats per minute after the subject was standing for at least 2-4 minutes compared to the heart rate measured in the supine position will also be summarized. Summaries will be presented over time and postdose overall.

Note: The categorization of orthostatic effects is intended for the data analysis and reporting of group effects and does not constitute guidance as to whether individual assessments reflect clinically meaningful changes (see [Section 13.1.1](#), Objective Findings for the protocol definition of clinically significant abnormal objective findings).

14.7.9. Physical and Neurological Examinations

The physical and neurological examinations of subjects at beginning of the study and end of study will be summarized by presenting the number and percentage of subjects with normal and abnormal findings in each body area (skin/extremities, EENT, head/neck, etc.).

14.7.9.1. Body Weight

In addition to descriptive summaries of body weight measures and changes from baseline for each assessment timepoint, the percent of subjects with increase of body weight $\geq 7\%$ from baseline will be summarized by timepoint and overall postdose.

14.7.10. Concomitant Medication

Other than the study drug, any medication taken by subjects during the course of the study will be considered concomitant. The number and percentage of subjects using each concomitant medication will be summarized according to the WHODRUG preferred term. Subjects with multiple uses of a concomitant medication will be counted once for a given PT.

14.7.11. Columbia-Suicide Severity Tracking Scale

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

14.7.12. Efficacy Analysis

All efficacy endpoints will be summarized descriptively for the planned treatment received in Protocol 093-050. Changes in efficacy parameters will be calculated with reference to the baseline period of Protocols 093-045 or 093-046.

Time on eslicarbazepine acetate monotherapy will be calculated from the first monotherapy dose in 093-045 or 093-046 to the last known dose of eslicarbazepine acetate monotherapy in 093-050. Median time and 95% CI will be estimated using Kaplan Meier time to event methods. Subjects who were still on eslicarbazepine acetate monotherapy at the end of study will be censored at the end of study. Subjects who dropped out the study while receiving monotherapy treatment will be censored at the time of the dropout. Change in dosage levels from 093-045 or 093-046, dosage changes during 093-050, and the time gap between the parent studies and the extension study will be ignored.

Response rate and seizure frequency reduction will be calculated with reference to the baseline period of Protocols 093-045 or 093-046. Seizure frequency during the 1 year open label period and during 3 month visit windows (V1 to V4 as the first 3 month period) will be standardized to 28 day rate. The standardized seizure frequency and changes from baseline will be summarized overall for the 1-year study period and for each 3 month visit window. Responder is defined as subjects who have $\geq 50\%$ reduction in standardized seizure frequency over baseline. The

proportion of responders will be summarized by overall study period and by 3 month visit window. These analyses will be also conducted by dose level received in 093-045 or 093-046.

Seizure-free subjects will be computed in every 3-month interval defined above during the study period.

Proportion (%) of subjects seizure-free during study period, and completion rate (proportion [%] of subjects completing the one-year treatment) will be provided.

Standardized seizure frequency will be calculated for each seizure type during the open-label period and each 3-month visit window.

Treatment retention time (time to withdrawal due to lack of efficacy or adverse events) will be estimated using KM methods. The time will be calculated from the first dose of eslicarbazepine acetate monotherapy in 093-045 or 093-046 to the last known dose of open-label eslicarbazepine acetate in 093-050. The time may include taking eslicarbazepine acetate concomitantly with other AEDs. Subjects who are still taking eslicarbazepine acetate at the end of study will be censored at the end of study.

Change in total score from Visit 2 (Day 0) of Protocols 093-045 or 093-046 to end of study treatment (Visit 7, Month 12) in QOLIE-31 will be summarized.

The total MADRS score will be summarized descriptively and the change in the total score will be summarized. In addition, change in total score from Visit 2 (Day 0) of Protocols 093-045 or 093-046 to end of study treatment (Visit 7, Month 12) in MADRS in those subjects with a MADRS score of ≥ 14 at screening visit of the present study.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Study monitoring is detailed in Appendix I (see [section 21.6](#)).

15.2. Audits and Inspections

The study audit process is detailed in Appendix I (see [section 21.6](#)).

15.3. Institutional Review Board

IRB is detailed in Appendix I (see [section 21.2](#)).

16. QUALITY CONTROL AND QUALITY ASSURANCE

Quality control and quality assurance are detailed in Appendix I (see [Sections 21.1](#) and [21.6](#)).

17. ETHICS

17.1. Ethics Review

17.2. Ethical Conduct of the Study

The Investigator agrees that the study will be conducted according to the protocol, the US Code of Federal Regulations, the principles of Good Clinical Practice (GCP), the World Medical Association Declaration of Helsinki (1989), and the International Conference on Harmonization (ICH) Guidelines. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

The Investigator must sign and return to the Sponsor or its representative the "Study Acknowledgment" page and provide a copy of a current curriculum vitae, including copy of current medical license. As this study is conducted under an Investigational New Drug (IND), the Investigator must sign and return a completed Form United States Food and Drug Administration (FDA) 1572 "Statement of Investigator" to the Sponsor or its representative.

The ethical and regulatory obligations of the Investigator are detailed in Appendix I.

17.3. Written Informed Consent

The informed consent process is detailed in Appendix I (see [Section 21.3](#)).

18. DATA HANDLING AND RECORDKEEPING

18.1. Computerized Systems

A list of the computerized systems that will be used to create, modify, maintain, archive, retrieve, or transmit source data are listed in [Appendix IX](#), per the Guidance for Industry Computerized Systems Used in Clinical Investigations, May 2007.

18.2. Inspection of Records

The inspection of records is detailed in Appendix I (see [Section 21.11](#)).

18.3. Retention of Records

The retention of records is detailed in Appendix I (see [Section 21.10](#)).

19. STUDY ACKNOWLEDGMENT

I have read the foregoing Protocol No. 093-050 “Long-Term Eslicarbazepine Acetate Extension Study” Version 6.0, and agree that it contains all necessary details for conducting this 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. REFERENCES

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21. APPENDIX I. ETHICAL AND REGULATORY OBLIGATIONS

21.1. Study Conduct

The Investigator agrees that the study will be conducted according to the principles of Good Clinical Practice (GCP), the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.

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 current audits, and will demonstrate due diligence in recruiting and screening study subjects.

The Investigator must sign and return to CRO/Sponsor the "Study Acknowledgment" page and provide a copy of current curriculum vitae, including a copy of a current medical license, current DEA license, where applicable, and financial disclosure. In countries where medical licensure is not issued, the following documentation is acceptable, as applicable:

- Registration number/stamp with a registration number stated on curricula vitae (CV)
- Appropriate diploma number stated on CV
- Copy of the diploma

For all studies conducted under an IND, the Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to CRO/Sponsor.

21.2. Institutional Review Board or Independent Ethics Committee

Before initiation of the study, the Investigator/CRO must obtain approval or favorable opinion of the research protocol, informed consent form, and any advertisement for subject recruitment, from an IRB or IEC complying with the provisions specified in 21 CFR Part 56 or in ICH GCP, as applicable, and applicable pertinent government regulations. The Investigator must assure IRB or IEC compliance with the applicable regulations.

A copy of written IRB or IEC approval or favorable opinion of the protocol, informed consent form and advertising (if applicable) must be provided to CRO/Sponsor prior to initiation of the study. The approval or favorable opinion letter must be signed by the IRB or 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 or IEC complies with the requirements in 21 CFR Part 56 for a study conducted under an IND or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not exceeding one year or otherwise specified by the IRB or 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 or other safety information reported from CRO/Sponsor in accordance with 21 CFR 312.66, or when dictated by applicable local regulations (ie Directive 2001/20/EC), the Sponsor/CRO is responsible for reporting to the IEC (eg, reporting of serious AEs).

21.3. Informed Consent

The Investigator will prepare the informed consent form and provide the form to CRO/Sponsor for approval prior to submission to the IRB or IEC. CRO/Sponsor may provide a template informed consent form to be qualified by each research facility to conform to local requirements. All informed consent forms must contain the minimum elements as mandated by the FDA or governing regulatory authority and ICH guidelines and will be subject to CRO/Sponsor' approval as well as IRB or IEC approval. CRO/Sponsor may submit informed consent forms to a central IRB or IEC for review and approval or favorable opinion contingent upon prior Investigator permission and review.

Before recruitment and enrollment, each prospective candidate will be given a full explanation of the study, allowed to read the approved informed consent form (or assent form for prospective candidates <18 years of age) 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 individual (or parent or legal guardian for individuals <18 years of age) understands the implications of participating in the study, the subject will be asked to give consent (or assent for subjects <18 years of age) to participate in the study by signing the informed consent/assent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review and regulatory inspection. The Investigator will provide a copy of the signed informed consent form to each subject. For subjects <18 years the parent or legal guardian will be required to provide written informed consent.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the informed consent/assent form must be revised, submitted to the IRB or IEC for review and approval or favorable opinion. The revised informed consent/assent form must be used to obtain consent/assent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent/assent form must be used to obtain consent/assent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the amendment.

21.4. Subject Privacy

The Sponsor's staff or any designees affirm and uphold the subject's confidentiality. Throughout this study, all data forward to the Sponsor will be identified only by an identification number. The Investigator agrees that its representatives, its designee, representatives of the relevant IRB/IEC or representatives of the regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, clinical laboratory test result reports, ECG reports, admission/discharge

summaries for hospital admissions occurring during a subject's study participation and autopsy reports for deaths occurring during the study).

For the studies conducted in the US, in accordance with the Healthcare Information Portability and Accountability Act of 1996, the Investigator will prepare a privacy authorization form and provide the form to CRO/Sponsor for approval prior to submission to the IRB/IEC or to a Privacy Board. CRO/Sponsor may provide a template privacy authorization form to be qualified by each research facility to conform to local requirements. The content of the privacy authorization form must comply with the regulations governing the authorization. All prospective study candidates will be given full explanation of the privacy authorization form, allowed to read the approved form, and be provided the opportunity to ask any questions. Once all questions have been answered and the Investigator is assured that the individual understands the implications of the privacy authorization form, the subject will be asked to sign the privacy authorization. The authorization remains in effect until revoked by the subject. The Investigator will provide a copy of the signed privacy authorization form to each subject. Subjects who do not sign the privacy authorization form will not be permitted to participate in the study.

21.5. Protocol Amendments and Emergency Deviations

Changes to the research covered by this protocol must be implemented by formal protocol amendment. Amendments to the protocol may be initiated by the Sponsor or at the request of the Investigator. In either case, a formal amendment cannot be initiated until the Sponsor has approved it, the Investigator has signed it off, and it has been reviewed and has received approval or favorable opinion by the IRB or IEC.

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

21.6. Monitoring and Auditing of the Study

A clinical monitor, whether an employee of the Sponsor or its designated representative, has the obligation to follow this study closely. In doing so, the monitor will visit the clinical study sites at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. Quality assurance auditors, whether an employee of the Sponsor or its designated representative, may evaluate the conduct of the study by the clinical study sites. These parties must have access to any and all study reports and source documentation, regardless of location and format. The Sponsor audit reports will be kept highly confidential.

21.7. Study Documentation

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

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

The CRO/Sponsor will supply electronic case report forms (eCRFs). All requested information must be entered on the eCRFs. If an item is not available or is not applicable, this fact should be indicated; do not leave a space blank. Each set of completed eCRFs must be reviewed, electronically signed and dated by the Investigator.

21.8. Laboratory Certification and Normal Values

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

21.9. Drug Accountability

The Investigator is responsible for storing the drug in a secure location and for maintaining adequate records of drug disposition that includes the dates, quantity, and use by subjects. If the investigation is terminated, discontinued, suspended or completed, all unused supplies of drug will be returned to the Sponsor, unless other instructions are provided in writing by CRO/Sponsor.

The drug will not be dispensed to any person who is not a study subject under this protocol.

If a drug is subject to the Controlled Substances Act or other similar local regulations, the Investigator shall take adequate precautions, including storage of the study drug in a securely locked cabinet, or other enclosure, access to which is limited.

21.10. Records Retention

The Investigator agrees to retain study records for the time periods stated below. The Investigator agrees to contact CRO/Sponsor before destroying any study documentation. Should the Investigator leave the site at which the study was conducted, CRO/Sponsor will be contacted regarding the disposition of document storage.

Records will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

Dates marking the beginning of the final record retention periods will be sent in writing from CRO/Sponsor. If an Investigator withdraws from the study (eg, relocation), the records will be transferred to a mutually agreed upon designee (ie, another Investigator). This transfer is subject to Sponsor approval and will be documented in writing and a copy sent to the Sponsor.

Electronic Data Capture Data Archiving:

In compliance with data retention requirements and after the capture phase of the study is complete; the site will receive the study and system documentation and a copy of all eSource and study data from EDC vendors. The vendors shall certify the integrity of the copy (certified copy) and send it on commonly readable storage material (currently CD ROM). This read-only archive will be retained, protected and made accessible by the site throughout the required retention period.

21.11. Inspection of Records

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

21.12. Financial Disclosure

Prior to the start of the study, Investigators will release sufficient and accurate financial information that permits CRO/Sponsor to demonstrate that an Investigator and all sub-Investigators listed on the FDA Form 1572, if appropriate, have no personal or professional financial incentive regarding the future approval or disapproval of the study drug such that his or her research might be biased by such incentive. Investigators will provide an update of the above financial information at the end of the study and one year following the end of the study.

22. APPENDIX II. CLINICAL LABORATORY TESTS

HEMATOLOGY^a

1. Total WBC Count
2. Differential:
 - Neutrophils
 - Lymphocytes
 - Monocytes
 - Eosinophils
 - Basophils
3. Hemoglobin
4. Hematocrit
5. RBC Count
6. Platelet Count

QUALITATIVE URINALYSIS^a

1. Glucose
2. Ketones
3. Protein
4. Blood
5. pH
6. Leukocyte esterase
7. Urobilinogen
8. Nitrites

QUANTITATIVE URINALYSIS

1. Microscopic Examination

DRUG SCREENING^b

1. Barbiturates
2. Benzodiazepines
3. Cannabinoids
4. Cocaine
5. Amphetamines
6. Opiates

BLOOD CHEMISTRIES^a

1. Electrolytes:
 - Bicarbonate (HCO₃)
 - Calcium (Ca)
 - Chloride (Cl)
 - Phosphorus (P)
 - Potassium (K)
 - Sodium (Na)
 - Magnesium (Mg)
2. Enzymes:
 - Alkaline Phosphatase (ALP)
 - Aspartate aminotransferase (AST)
 - Alanine aminotransferase (ALT)
 - Creatinine phosphokinase (CPK)
3. Other:
 - Albumin
 - Bilirubin (Total, Direct, Indirect)
 - Creatinine
 - Glucose
 - Protein (Total)
 - Blood Urea Nitrogen (BUN)
 - Uric Acid

OTHER TESTS

1. Coagulation (PT/INR, PTT)
2. Serum Pregnancy (β-HcG) (female subjects of child bearing potential only)
3. Thyroid (free T₃, free T₄, and TSH)
4. Bone Turnover Markers (serum 25-OHD, PTH, osteocalcin, bone-specific ALP, and urinary NTx)
5. Lipid Panel (cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides)^a

Abbreviations: CPK=creatinine phosphokinase; 25-OHD=25-hydroxyvitamin D; HDL=high-density lipoprotein; INR=international normalized ratio; LDL=low-density lipoprotein; PT=prothrombin time; PTH=parathyroid hormone; PTT=partial thromboplastin time; NTx=N-telopeptides of type I collagen cross-links; TSH=thyroid stimulating hormone; V=visit; WBC=white blood cells.

a. Fasting labs.

b. Performed at Visit 1 only. Visit 1 of this study corresponds to Visit 9 of Protocols 093-045 and 093-046. The following procedures are also performed at Visit 9 of Protocols 093-045 and 093-046 and therefore do not have to be duplicated in the present study. The results are applicable to this study as well.

Laboratory reports will be initialed and dated on all pages by a 1572-listed investigator (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.

Abnormal laboratory findings will be rated according to the following scale:

- 1 = Deviation from reference range and not clinically significant; not related to underlying condition or disease;
- 2 = Deviation from reference range and not clinically significant; related to any underlying condition or disease; or
- 3 = Deviation from reference range and clinically significant (to be followed until normalized or new baseline; if post-screening, a corresponding AE must be recorded).

A positive drug screen does not require a deviation code.

23. APPENDIX III. CARDIAC SAFETY MONITORING/ECG

I. Requirements for Testing

ECG equipment and supplies will be provided by the ECG Core Lab and should be used for all in-clinic protocol ECG assessments.

All 12-lead ECGs will be recorded in the same manner.

- The site personnel must be able to demonstrate documentation of adequate training in performing ECGs on the specific ECG equipment used in this protocol that is provided by the ECG Core Lab.
- To the extent possible, the same ECG machine and personnel should be used for the subject's period of participation in the study.
- All ECGs will be recorded with at least one 10-second single-lead rhythm strip recorded from Lead II.
- All ECGs will be electronically transmitted to the ECG Core Lab daily.

II. Subject Restrictions and Instructions

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

III. Reporting

- It is the responsibility of the Investigator to perform a safety review of all ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility or continuance in the study.
- All ECGs waveforms and over-read (if applicable) reports will be reviewed, signed and dated by an Investigator listed on the FDA 1572 (MD or DO). The same Investigator should review all ECG reports for a given subject whenever possible.
- For all ECGs, a report will be provided by the cardiac safety vendor to the site for review and signature.
- Waveforms and over-read (if applicable) reports will be kept with the subject's source documentation and/or eCRF unless it is specified otherwise.
- Original waveforms and over-read (if applicable) reports will be retained at the site.

IV. Data Standardization

All ECGs will be centrally over-read (except for the post-1-year EOS/ET ECG, if performed) and interpreted using standard procedures at the ECG Core Lab.

24. APPENDIX IV. DEFINITIONS FOR REPORTING ADVERSE EVENTS

The Investigator must assess the severity of the adverse event using the following:

- **Mild** - awareness of event but easily tolerated.
- **Moderate** - discomfort enough to cause some interference with normal activity.
- **Severe** - inability to carry out usual activity.

The Investigator must assess the relationship of the adverse event to the study drug using the following:

- **Not related** – improbable temporal relationship and is plausibly related to other drugs or underlying disease.
- **Unlikely** – occurred within a reasonable time frame after administration/discontinuation of study drug, but there is a likely association of an intercurrent/underlying medical condition or other drugs.
- **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.
- **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.

Frequency will be defined using the following terms and definitions:

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

The action taken regarding study drug will be defined as follows:

- **Dose not changed** – no change
- **Dose interrupted** – study drug stopped temporarily.
- **Dose modified** – study drug decreased or increased.
- **Dose withdrawn** – study drug stopped permanently.

25. APPENDIX V. STRUCTURED INTERVIEW GUIDE FOR THE MONTGOMERY-ASBERG DEPRESSION RATING SCALE (MADRS) (SIGMA)

The rating should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on predefined scale steps (0, 2, 4, 6) or between them (1, 3, 5).

It is important to remember that it is only on rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patient all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice.

The scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

Item List

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

1. Apparent Sadness

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rated by depth and inability to brighten up.

- 0 No sadness.
- 1
- 2 Looks dispirited but does brighten up without difficulty.
- 3
- 4 Appears sad and unhappy most of the time.
- 5
- 6 Looks miserable all the time. Extremely despondent.

2. Reported sadness

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or the feeling of being beyond help and without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

- 0 Occasional sadness in keeping with the circumstances.
- 1
- 2 Sad or low but brightens up without difficulty.
- 3
- 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
- 5
- 6 Continuous or unvarying sadness, misery or despondency.

3. *Inner tension*

Representing feeling of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

- 0 Placid. Only fleeting inner tension.
- 1
- 2 Occasional feelings of edginess and ill-defined discomfort.
- 3
- 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
- 5
- 6 Unrelenting dread or anguish. Overwhelming panic.

4. *Reduced sleep*

Representing the experience of reduced duration or depth of sleep compared with the subject's own normal pattern when well.

- 0 Sleeps as usual.
- 1
- 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- 3
- 4 Sleep reduced or broken by at least two hours.
- 5
- 6 Less than two or three hours sleep.

5. *Reduced appetite*

Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- 0 Normal or increased appetite.
- 1
- 2 Slightly reduced appetite.
- 3
- 4 No appetite. Food is tasteless.
- 5
- 6 Needs persuasion to eat at all.

6. *Concentration difficulties*

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

- 0 No difficulties in concentrating.
- 1
- 2 Occasional difficulties in collecting one's thoughts.
- 3
- 4 Difficulties in concentration and sustaining thought which reduces ability to read or hold a conversation.
- 5
- 6 Unable to read or converse without great difficulty.

7. *Lassitude*

Representing a difficulty getting started or slowness initiating and performing everyday activities.

- 0 Hardly any difficulty in getting started. No sluggishness.
- 1
- 2 Difficulties in starting activities.
- 3
- 4 Difficulties in starting simple routine activities which are carried out with effort.
- 5
- 6 Complete lassitude. Unable to do anything without help.

8. *Inability to feel*

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- 0 Normal interest in the surroundings and in other people.
- 1
- 2 Reduced ability to enjoy usual interests.
- 3
- 4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances.
- 5
- 6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. *Pessimistic thoughts*

Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

- 0 No pessimistic thoughts.
- 1
- 2 Fluctuating ideas of failure, self-reproach or self-depreciation.
- 3
- 4 Persistent self-accusations, or definite but still rational ideas of guilt or sin.
Increasingly pessimistic about the future.
- 5
- 6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. *Suicidal thoughts*

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts and preparations for suicide.

Suicidal attempts should not in themselves influence the rating.

- 0 Enjoys life or takes it as it comes.
- 1
- 2 Weary of life. Only fleeting suicidal thoughts.
- 3
- 4 Probably better off dead. Suicidal thoughts are common and suicide is considered as a possible solution, but without specific plans or intention.
- 5
- 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Reproduced from: A new depression scale designed to be sensitive to change. S.A. Montgomery & M. Åsberg, *British Journal of Psychiatry* (1979), 134, 382-389. © 1979 The Royal College of Psychiatrists.

26. APPENDIX VI. 31-ITEM QUALITY OF LIFE IN EPILEPSY SCALE (QOLIE-31)

QUALITY OF LIFE IN EPILEPSY QOLIE-31 (Version 1.0)

Patient Inventory

Today's Date ___/___/___

Patient's Name _____

Patient's ID# _____

Gender: Male Female

Birthdate ___/___/___

Do Not
Write in
This Space

INSTRUCTIONS

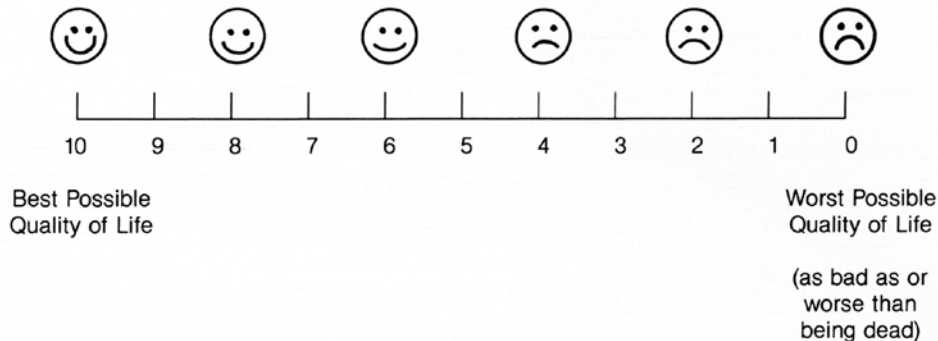
This survey asks about your health and daily activities. **Answer every question** by circling the appropriate number (1, 2, 3, ...).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need help reading or marking the form.

1. Overall, how would you rate your quality of life?

(Circle one number on the scale below)



These questions are about how you **FEEL** and how things have been for you during the **past 4 weeks**. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks** . . .

(Circle one number on each line)

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 This Space

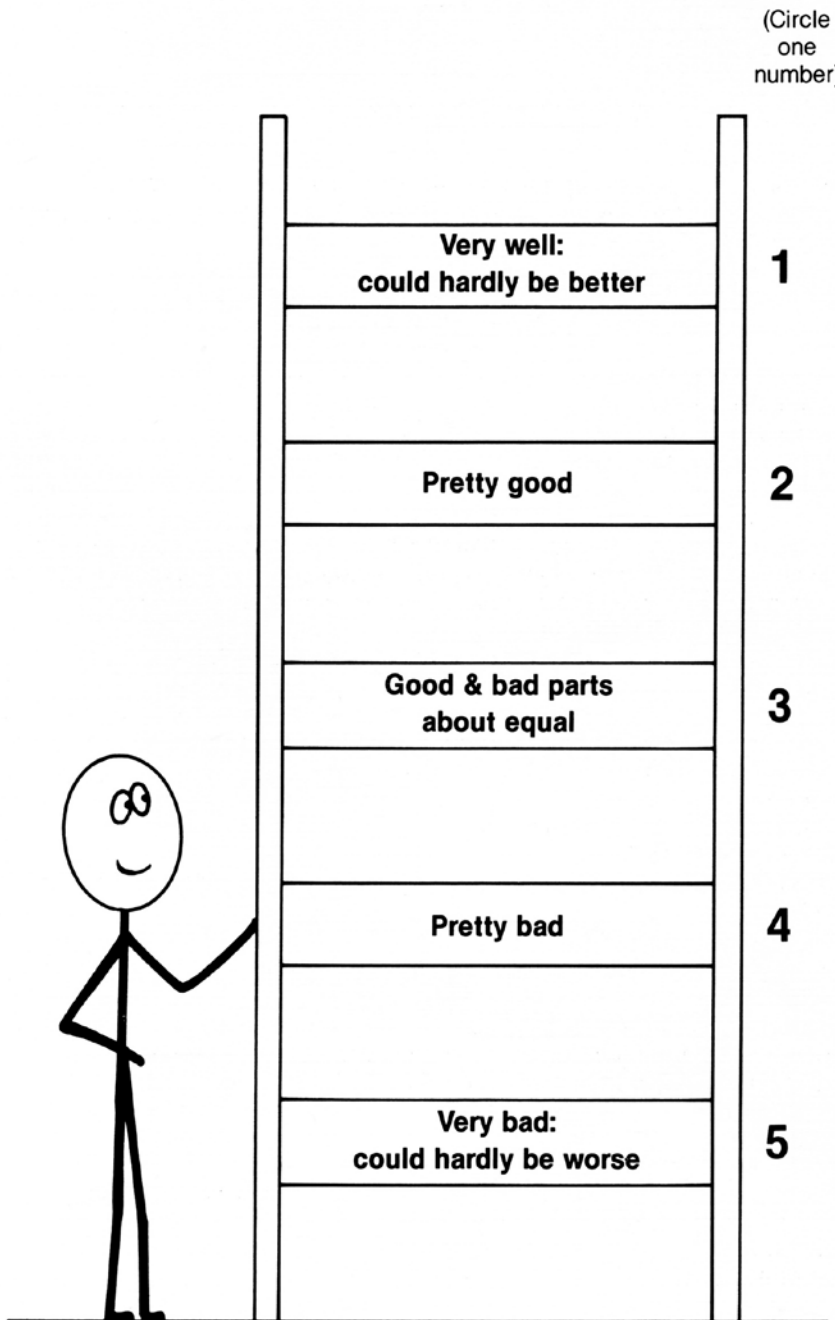
		All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
2.	Did you feel full of pep?	1	2	3	4	5	6
3.	Have you been a very nervous person?	1	2	3	4	5	6
4.	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
5.	Have you felt calm and peaceful?	1	2	3	4	5	6
6.	Did you have a lot of energy?	1	2	3	4	5	6
7.	Have you felt downhearted and blue?	1	2	3	4	5	6
8.	Did you feel worn out?	1	2	3	4	5	6
9.	Have you been a happy person?	1	2	3	4	5	6
10.	Did you feel tired?	1	2	3	4	5	6
11.	Have you worried about having another seizure?	1	2	3	4	5	6
12.	Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?	1	2	3	4	5	6
13.	Has your health limited your social activities (such as visiting with friends or close relatives)?	1	2	3	4	5	6

14. How has the **QUALITY OF YOUR LIFE** been during the **past 4 weeks** (that is, how have things been going for you)?

*Do Not
Write in
This Space*

(Circle one number)

Very well: could hardly be better	1
Pretty good	2
Good & bad parts about equal	3
Pretty bad	4
Very bad: could hardly be worse	5



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Copyright 1993, RAND. All rights reserved. The QOLIE-31 was developed in cooperation with Professional Postgraduate Services, a division of Physicians World Communications Group, and the QOLIE Development Group.

The following question is about **MEMORY**.

(Circle one number)

Do Not
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 This Space

	Yes, a great deal	Yes, somewhat	Only a little	No, not at all
15. In the past 4 weeks, have you had any trouble with your memory?	1	2	3	4

Circle one number for **how often** in the **past 4 weeks** you have had trouble *remembering* or **how often** this memory problem has interfered with your normal work or living.

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
16. Trouble remembering things people tell you	1	2	3	4	5	6

The following questions are about **CONCENTRATION** problems you may have. Circle one number for **how often** in the **past 4 weeks** you had trouble concentrating or **how often** these problems interfered with your normal work or living.

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
17. Trouble concentrating on reading	1	2	3	4	5	6
18. Trouble concentrating on doing one thing at a time	1	2	3	4	5	6

The following questions are about problems you may have with certain **ACTIVITIES**. Circle one number for **how much** during the **past 4 weeks** your epilepsy or antiepileptic medication has caused trouble with . . .

	A great deal	A lot	Somewhat	Only a little	Not at all
19. Leisure time (such as hobbies, going out)	1	2	3	4	5
20. Driving	1	2	3	4	5

The following questions relate to the way you **FEEL** about your **seizures**.
 (Circle one number on each line)

*Do Not
 Write in
 This Space*

	Very fearful	Somewhat fearful	Not very fearful	Not fearful at all
21. How fearful are you of having a seizure during the next month?	1	2	3	4

	Worry a lot	Occasionally worry	Don't worry at all
22. Do you worry about hurting yourself during a seizure?	1	2	3

	Very worried	Somewhat worried	Not very worried	Not at all worried
23. How worried are you about embarrassment or other social problems resulting from having a seizure during the next month?	1	2	3	4

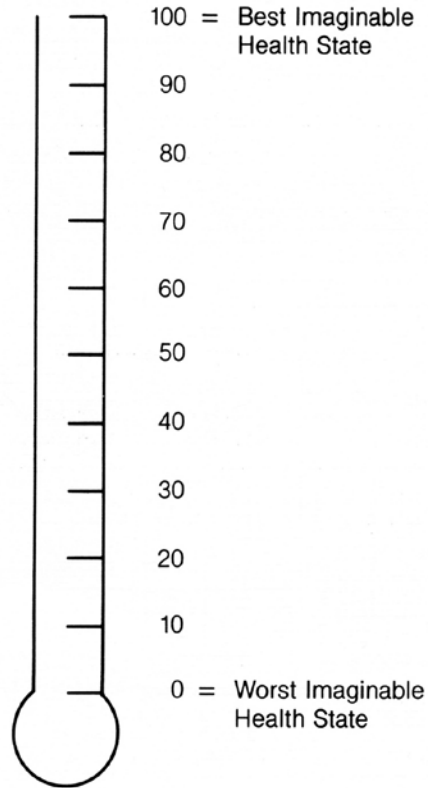
24. How worried are you that medications you are taking will be bad for you if taken for a long time?	1	2	3	4
---	---	---	---	---

For each of these **PROBLEMS**, circle one number for **how much they bother you** on a scale of 1 to 5 where 1 = Not at all bothersome, and 5 = Extremely bothersome.

	Not at all bothersome				Extremely bothersome
25. Seizures	1	2	3	4	5
26. Memory difficulties	1	2	3	4	5
27. Work limitations	1	2	3	4	5
28. Social limitations	1	2	3	4	5
29. Physical effects of antiepileptic medication	1	2	3	4	5
30. Mental effects of antiepileptic medication	1	2	3	4	5

31. How good or bad do you think your health is? On the thermometer scale below, the best imaginable state of health is 100 and the worst imaginable state is 0. Please indicate how you feel about your health by circling one number on the scale. **Please consider your epilepsy as part of your health when you answer this question.**

*Do Not
Write in
This Space*



Comments (if any)

Copyright 1993, RAND. All rights reserved. The QOLIE-31 was developed in cooperation with Professional Postgraduate Services, a division of Physicians World Communications Group, and the QOLIE Development Group.

Development of the QOLIE-89, QOLIE-31 and QOLIE-10 inventories was supported by an unrestricted research grant from Wallace Laboratories, and administered by Professional Postgraduate Services, a division of Physicians World Communications Group.

27. **APPENDIX VII. COLUMBIA-SUICIDE SEVERITY RATING
SCALE (C-SSRS)**

**COLUMBIA-SUICIDE SEVERITY
RATING SCALE
(C-SSRS)**

Baseline

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.;
Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.*

Disclaimer:

*This scale is intended for use by trained clinicians. The questions contained in the
Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the
determination of the presence of suicidality depends on clinical judgment.*

*Definitions of behavioral suicidal events in this scale are based on those used in
The Columbia Suicide History Form, developed by John Mann, MD and Maria
Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders
(CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York,
NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal
behavior: utility and limitations of research instruments. In M.B. First [Ed.]
Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric
Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact
posnerk@childpsych.columbia.edu*

SUICIDAL IDEATION					
<p><i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i></p>	Lifetime: Time He/She Felt Most Suicidal				
<p>1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan. <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it". <i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to "I have the thoughts but I definitely will not do anything about them". <i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				

INTENSITY OF IDEATION		
<i>The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.</i>		Most Severe
Most Severe Ideation: _____ <div style="display: flex; justify-content: space-around;"> <i>Type # (1-5)</i> <i>Description of Ideation</i> </div>		
Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day		_____
Duration <i>When you have the thoughts, how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time		_____
Controllability <i>Could /can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts		_____
Deterrents <i>Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply; wish to die only		_____
Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (2) Mostly to get attention, revenge or a reaction from others. (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.		_____

SUICIDAL BEHAVIOR <i>(Check all that apply, so long as these are separate events; must ask about all types)</i>	Lifetime
<p>Actual Attempt: A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.</p> <p>Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? <i>What did you do?</i> <i>Did you _____ as a way to end your life?</i> <i>Did you want to die (even a little) when you _____?</i> <i>Were you trying to end your life when you _____?</i> <i>Or did you think it was possible you could have died from _____?</i> Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts _____</p> <p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</p> <p>Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.</p> <p>Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted _____</p>
<p>Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.</p> <p>Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted _____</p>
<p>Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note).</p> <p>Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>
<p>Suicidal Behavior: Suicidal behavior was present during the assessment period?</p>	<p>Yes No <input type="checkbox"/> <input type="checkbox"/></p>

<i>Answer for Actual Attempts Only</i>	Most Recent Attempt	Most Lethal Attempt	Initial/First Attempt
<p>Actual Lethality/Medical Damage:</p> <p>0. No physical damage or very minor physical damage (e.g. surface scratches).</p> <p>1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains).</p> <p>2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).</p> <p>3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).</p> <p>4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).</p> <p>5. Death</p>	Date		
	Enter #		
<p>Potential Lethality: Only Answer if Actual Lethality=0</p> <p>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).</p> <p>0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care</p>	Date		
	Enter #		

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.;
Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.*

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

*Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION					
<p><i>Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.</i></p>	Since Last Visit				
<p>1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, "I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it". <i>Have you been thinking about how you might do this?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to "I have the thoughts but I definitely will not do anything about them". <i>Have you had these thoughts and had some intention of acting on them?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				
<p>5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i></p> <p>If yes, describe:</p>	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	No				
<input type="checkbox"/>	<input type="checkbox"/>				

SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)	Since Last Visit
<p>Actual Attempt: A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? <i>What did you do?</i> Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent) If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts</p> <p>_____</p> <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</p> <p>Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of interrupted</p> <p>_____</p>
<p>Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted</p> <p>_____</p>
<p>Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p>Suicidal Behavior: Suicidal behavior was present during the assessment period?</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p>Completed Suicide:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>

Answer for Actual Attempts Only		Most Lethal Attempt
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; <i>medical</i> hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; <i>medical</i> hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Date	
	Enter #	
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	Date	
	Enter #	

28. APPENDIX VIII. MEDICAL EVENT CALENDAR

The Medical Event Calendar (MEC) is used to track a subject's health status while away from clinic in an efficient and possibly more reliable manner than in-clinic questioning that relies solely on subject recollection. They will be provided by Sunovion Pharmaceuticals Inc. for each study subject and are to be used throughout the study. While at home, subjects will daily record:

- Any new medications taken not already reported to clinic staff.
- Any emergent symptoms that occur, regardless of their relationship or the period of study participation.

Study Staff will review, sign, and date the MEC at the beginning of each clinic visit.

Emergent AEs should be recorded onto the eCRF using medically correct terminology and not necessarily using the verbatim subject report from the MEC. The relationship between an MEC entry and what is recorded in the eCRF should be noted in the source documentation if the subject verbatim term is not used in the eCRF.

Symptoms that are consistent in nature, frequency and severity with conditions noted in the pre-study Medical History do not need to be recorded on the MEC and will not be captured on the AE eCRF page. However, if a symptom is recorded on the MEC that is greater in frequency or intensity from that reported pre-study, this will be included in the eCRF. When possible, diagnoses should be recorded on the AE eCRF page and not a list of the individual symptoms comprising the diagnosis. For example, MEC symptoms recorded as "chills", "headache", "fever" which occur in conjunction with each other should be recorded in the eCRF as "influenza" after discussion of the symptoms with the subject and based on the appropriate medical interpretation.

A sample is attached on the following page.

Month Year

S _____ Initials: _____ Investigator _____ Site# _____ Study _____ - _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
This calendar is being used to help the study staff keep track of how you are feeling during the course of the study. The study coordinator may ask you questions to explain or investigate further what you have written on this calendar. If you are unsure about what you should write down, please enter it on this sheet and discuss with your study coordinator at your next visit. Please write down any medications you take (prescription or over-the-counter), on the day you take it. Record the dose (eg, 250 mg), how much (eg, 2 tabs), and the time it was taken. Medication that you take regularly and have already told the study staff about does not need to be re-written. But, if you change how you take one of your regular medications, please record the change here.						___ / ___ <input type="checkbox"/> No Entries
___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries
___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries
___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries
___ / ___ <input type="checkbox"/> No Entries	___ / ___ <input type="checkbox"/> No Entries					

Please write down any illnesses, symptoms, or medical conditions that you experience – especially ones you have never experienced before. Write down both temporary things (eg, stomach ache, headache) and longer illnesses (eg, chest cold, sprained ankle). Also, please be sure to write down if a symptom, illness, or medical condition you have experienced before becomes worse or happens more often.

 Initials of Reviewing Staff Person

 Date

Reminder: if you have been hospitalized or seen in an Emergency Room since your last study visit, please indicate.

29. APPENDIX IX. COMPUTERIZED SYSTEMS USED FOR SOURCE DATA

The following table identifies each step at which a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit source data.

Protocol Step^a	System Type or Description
A	EDC (Inform)
B	LIMS
C	Core Lab Overread ^b
D	LIMS/Excel Spreadsheet
Statistical Analysis	SAS [®]
Abbreviations: EDC=Electronic Data Capture; LIMS=Laboratory Information Management System. a. A letter (eg, "A") identified in the Protocol Step column refers back to the Schedule of Assessment table. b. Not applicable for post-1-year EOS/ET ECG assessment, if performed.	

30. APPENDIX X. SEIZURE DIARY

Site ID:

SUBJECT SEIZURE DIARY

Year _____

Subject Number:

1. Take this diary home and use it every day to keep track of your seizures.
2. The research staff will review your seizures with you and will assign your symptoms to the appropriate Seizure Type below.
3. If you have a seizure, record the type of seizure (using the assigned code) on the diary.
4. If you do not have any seizures on that day, mark the 'no seizure' box.
5. The research staff will discuss your seizure diary with you during your regular telephone contacts.
6. Bring the seizure diary with you to every appointment.

Seizure Code: Description given by patient/caregiver (Seizure Type)

A:

B:

C:

D:

Example:

02/MAR
<input type="checkbox"/> No Seizures Today
A
C
A

Enter the day of the month (in 2 digit format) first, then the month abbreviation in 3-letter format.

Mark the no seizure box if you did not have any seizures that day.

If you had any seizures that day, write down seizure type by codes listed above. Please list each seizure separately, and in the order they occurred during the day.

If you have any additional comments, please use the space provided. Please indicate which day(s) and which seizure type(s) your comment(s) refer to.

Site ID:

Subject Number:

SUBJECT SEIZURE DIARY

Year _____

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures
____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures
____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures	____/____/____ <input type="checkbox"/> No Seizures

Comments:

 Initials of Reviewing Staff Person

 Date

31. APPENDIX XI. DIASTAT[®] (DIAZEPAM RECTAL GEL) DOSING CHART

12+ Years 0.2 mg/kg	
Weight (kg)	Dose (mg)
14 to 25	5
26 to 37	7.5
38 to 50	10
51 to 62	12.5
63 to 75	15
76 to 87	17.5
88 to 111	20

32. APPENDIX XII. DESCRIPTION OF TREATMENT OPTIONS IN COUNTRIES WHERE LORAZEPAM AS RESCUE MEDICATION IS NOT AVAILABLE

Rescue treatment for seizures requiring administration of benzodiazepines will use the treatment options as listed below *in order of preference*. The first listed treatment option should be selected that is approved by applicable regulatory bodies and in accordance with the standard-of-care in the country concerned.

Rescue Medication	Dose	Route	Comments
Lorazepam tablets	2 mg	oral	Prescription of 1 x 2 mg or 2 x 1 mg tablets as available
Diazepam tablets	5 mg	oral	--
Diazepam drops	5 mg	oral	--

33. APPENDIX XIII. DESCRIPTION OF TREATMENT OPTIONS IN COUNTRIES WHERE DIASTAT® (DIAZEPAM RECTAL GEL) AS EMERGENCY MEDICATION IS NOT AVAILABLE

Emergency treatment for breakthrough seizures (including repeated seizures and status epilepticus) requiring administration of benzodiazepines will use the treatments listed below *in order of preference*. The first listed treatment should be selected which is approved by applicable regulatory bodies in the patient's locale and/or based on the patient's condition.

Emergency Medication	Dose	Route	Comments
Diazepam rectal gel	0.2 mg/kg rounded to 2.5 mg increment	rectal	AcuDial® applicator allows person applying drug to select the prescribed dose.
Diazepam solution	--	rectal	Dose to be determined by investigator.
Diazepam tablets	5-10 mg	oral	--
Diazepam solutions	5-10 mg	intra muscular	Requires training of person administering drug. The Diazepam AutoInjector® delivers 10 mg in a single dose.
Diazepam drops	5-10 mg	oral	--

**34. APPENDIX XIV. PATIENT GLOBAL IMPRESSION (PGI)
SCALE**

Global Improvement	
Please rate your overall condition compared to before you started the clinical study.	<input type="checkbox"/> Very much improved <input type="checkbox"/> Improved <input type="checkbox"/> No change <input type="checkbox"/> Worse <input type="checkbox"/> Very much worse