



## **STATISTICAL ANALYSIS PLAN**

### **Long-Term Eslicarbazepine Acetate Extension Study**

**Protocol No. 093-050**

**Prepared by QuintilesIMS Inc.  
4820 Emperor Boulevard  
Durham, NC 27703  
USA**

**Prepared for  
Sunovion Pharmaceuticals Inc.  
84 Waterford Drive  
Marlborough, MA 01752  
USA**



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Statistical Analysis Plan Signature Page - Authors

Authored by:		Reviewed by:	
[Redacted]	22 May 2017	[Redacted]	23 MAY 2017
[Redacted]	Date	[Redacted]	Date
Biostatistician, II QuintilesIMS Inc.		Director, Biostatistics QuintilesIMS Inc.	

**Statistical Analysis Plan Signature Page - Approval**

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study

Approved by: [Redacted]		Approved by: [Redacted]	
[Redacted]	02 MAY 2017	[Redacted]	[Redacted]
Senior Director, Biostatistics Sunovion Inc.	Date	Head of Global Clinical Research Neurology Sunovion Inc.	Date
[Redacted]	5/25/17	[Redacted]	[Redacted]
Executive Project Director, Product Management Sunovion Inc.	Date	Senior Director, Medical Affairs Sunovion Inc.	Date

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### List of abbreviations and definition of terms

25-OHD	Serum 25-hydroxyvitamin D
AE	Adverse Event
AEDs	Anti-Epileptic Drugs
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per Minute
BUN	Blood Urea Nitrogen
eCRF	Electronic Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
EENT	Eyes, Ears, Nose, and Throat
ESL	Eslicarbazepine acetate
HDL	High Density Lipoprotein
INR	International Normalized Ratio
IPD	Important Protocol Deviation
ITT	Intent-to-Treat
LDL	Low Density Lipoprotein
MADRS	Montgomery-Asberg Depression Rating Scale
MEC	Medical Events Calendar
MedDRA	Medical Dictionary for Regulatory Affairs
N/A	Not Applicable
NTx	N-telopeptides of type I collagen cross-links
PCS	Potentially Clinically Significant
PGI	Patient Global Impression
PT	Prothrombin Time
PTH	Parathyroid Hormone
PTT	Partial Thromboplastin Time
QD	Once Daily
QOLIE	Quality of Life in Epilepsy
SAP	Statistical Analysis Plan
SOC	System Organ Class
SSF	Standardized Seizure Frequency
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization

## 1. Introduction

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol 093-050. It describes, in detail, the data and endpoints to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This Statistical Analysis and Reporting Plan (SAP) is based on protocol version 6.0, dated 7June2013.

## 2. Study objectives

The objective of this study is to 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.

### 2.1. Primary objective

To evaluate the 1-Year Open-Label Period and Post-1-Year Open-Label Period 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).

### 2.2. Secondary objectives

- To evaluate the maintenance of the therapeutic effects of eslicarbazepine acetate over a 1-Year Open-Label Period and Post-1-Year Open-Label Period.
- To evaluate the health-related quality-of-life, suicidality, and depressive symptoms over a 1-Year Open-Label Period and Post-1-Year Open-Label Period.

## 3. Study design

### 3.1. General Description

This 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 Open-Label Period with the option of continuing study drug treatment Post-1-Year Open-Label Period 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 Open-Label Period and a Post-1-Year Open-Label Period.



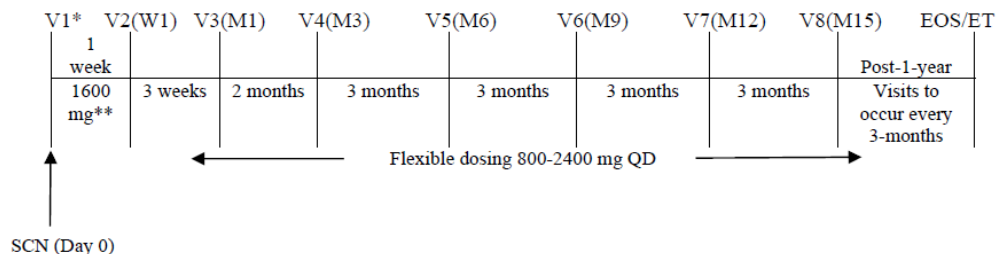
Subjects who enter the present study will receive a starting dose of 1600 mg QD of eslicarbazepine acetate, orally for 1 week at the start of the 1-Year Open-Label Period. The starting dose for subjects who had a dose reduction during participation in studies 093-045 or 093-046 will be 1200 mg and not 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 Open-Label Period part of the study will continue to receive the same dose of study drug that they received at Visit 7 (end of 1-Year Open-Label Period of treatment). The same dosing rules as in the 1-Year Open-Label Period part of the study are applicable in the Post-1-Year Open-Label Period 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 Open-Label Period and Post-1-Year Open-Label Period 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 Open-Label Period or Post-1-Year Open-Label Period 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 in the protocol.



### 3.2. 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.

### 3.3. Determination of Sample Size

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.

## 4. Changes in the Conduct of the Study or Planned Analysis

### 4.1. Changes in the Conduct of the Study

Six amendments have been incorporated into protocol 093-050 since final protocol.

### 4.2. Changes from Analyses Planned in the Protocol

The following change was made to the analysis planned in the protocol. This change was made prior to finalization of the SAP and prior to database lock.

The protocol in Section 7.2.3 indicates that the fraction of subjects who completed treatment at each visit post-1-year will be summarized. The change to this endpoint is that the fraction of subjects who completed treatment only for the entire post-1-year period will be summarized.



## 5. Efficacy and Safety Variables

### 5.1. Schedule of Evaluations

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

Author:



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Procedures	Visit 1/ SCN <sup>a</sup>	Visit 2	Visit 3	Visit 4	Visits 5 and 6	Visit 7	Post-1-year Visit 8 onwards	EOS/ET	Computer Systems <sup>c</sup>
	Day 0	Week 1	Month 1	Month 3	Months 6 and 9	Month 12	Month 15 onwards <sup>b</sup>		
Dispense Study Drug	X	X	X	X	X	X <sup>p</sup>	X		A
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 in protocol).
- 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 judgement 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. Every 6 months (i.e. Visits 7, 9, 11, 13, etc.).
- l. Only in subjects ≥18 years at time of signing informed consent in Protocols 093-045 or 093-046.
- m. Only for subjects who discontinue study during the post-1-year part of study.
- n. Fill out “since last visit” scale (Appendix VII in protocol).
- o. Only for subjects who discontinue study during the 1-year part of study.
- p. Only for subjects who continue into the post-1-year part of the study.

## 5.2. Efficacy Assessment and Endpoints

### 5.2.1. Assessments

Each subject will be instructed to keep a seizure diary and record information on all seizures for the first one-year of the study starting from Visit 1 (Screening) and ending at Visit 7. 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. At return visits 2 through 7, the seizure diary will be reviewed, and collected.

The 31-Item Quality of Life in Epilepsy Scale (QOLIE-31)<sup>1</sup> will be self-administered by only subjects who have completed 18 years of age at time of signing informed consent in Protocols 093-045 or 093-046.

The Montgomery-Asberg Depression Rating Scale (MADRS)<sup>2</sup> measures the severity of a subject's depressive symptoms. MADRS will be performed by a credentialed and trained MADRS rater.

The Patient Global Impression (PGI) scale measures the patient impression of improvement in disease. The PGI will be subject self-administered at all visits during the Post-1-Year Open-Label Period only. The 5 individual items will be summarized with descriptive statistics for each Post-1-Year Open-Label Period visit.

### 5.2.2. 1-Year Open-Label Period Efficacy Endpoints

#### 1. Time on eslicarbazepine acetate monotherapy

Time on eslicarbazepine acetate monotherapy during 1-Year Open-Label Period will be calculated from the date of the first eslicarbazepine acetate monotherapy dose in protocol 093-045 or 093-046 (Visit 6/Week 8) to the last known dose of eslicarbazepine acetate monotherapy during 1-Year Open-Label Period as follows;

- a. For a subject who added a non-rescue AED during 1-Year Open-Label Period, Time on Monotherapy during 1-Year Open-Label Period is calculated as the date of start a non-rescue AED during 1 Year Open-Label Period minus the date of the first monotherapy dose in protocol 093-045 or 093-046.
- b. For a subject who completed the 1-Year Open-Label Period, and did not add any non-rescue AED since the date of the first monotherapy dose in protocol 093-045 or 093-046, Time on Monotherapy during 1-Year Open-Label Period is calculated as the date of the last known dose during 1-Year Open-Label Period, minus the date of the first monotherapy dose in protocol 093-045 or 093-046, plus 1.
- c. For a subject who did not complete the 1-Year Open-Label Period, and did not add any non-rescue AED since the date of the first monotherapy dose in protocol 093-045 or 093-046, Time on Monotherapy during 1-Year Open-

Label Period is calculated as the date of the known dose before the withdrawal during 1-Year Open-Label Period, minus the date of the first monotherapy dose in protocol 093-045 or 093-046, plus 1.

**2. Seizure frequency**

Seizure frequency from the subject’s diary data will be evaluated by standardizing the sum of seizures to a frequency per 4 weeks (28 days). The standardized seizure frequency (SSF) for any given period (including baseline) will be calculated as:

$$\frac{\text{Total number of seizures reported in the diary during the interval of interest}}{\text{Number of days on study for the interval of interest}} \times 28 \text{ days}$$

The number of days on study for the interval of interest will be determined by:

$$\text{Visit Date of last visit during the interval of interest} - \text{Visit Date of first visit during the interval of interest}$$

**3. Relative change in seizure frequency from baseline**

Seizure frequency change from the baseline period will be evaluated by using SSF per 4 weeks (28 days). The baseline period is the period from Visit 1 to Visit 2 from Protocols 093-045 or 093-046.

The relative (%) change in SSF for any interval of interest (including baseline) will be calculated as:

$$\frac{(\text{SSF during the interval of interest}) - (\text{SSF during baseline period})}{\text{SSF during baseline period}} \times 100$$

Further the relative change from baseline will be categorized into:

- 100% Decrease
- ≥ 75% - < 100% Decrease
- ≥ 50% - < 75% Decrease
- 0% to < 50% Decrease
- > 0% to < 25% Increase
- ≥25% to <50% increase
- ≥50% to <100% increase
- ≥100 % increase

**4. Responder rate**

Responder is defined as having a ≥50% reduction in SSF from baseline.

The proportion will be calculated as the number of responders divided by the total number of subjects in the ITT population entering the period of interest.

**5. Seizure-free**

Subjects who did not have any seizure as per the seizure diary during that time period will be deemed seizure free, for the corresponding interval of interest. However, subjects who discontinue prior to Visit 7 will be considered not seizure-free for the interval when the discontinuation takes place and all subsequent intervals (even if the subjects are seizure-free at the time of discontinuation). That is, subjects must complete each interval of interest without any seizures to be considered seizure-free for each interval of interest.

The number and percent of seizure-free subjects will be presented for the interval of interest, for each interval the percent will be based out of the number of subjects in the ITT population entering each interval of interest.

**6. Seizure frequency by seizure type**

SSF will be calculated by seizure type using the same methods described in #2 of this section.

**7. Completion rates**

Study completion is defined as the proportion of subjects from the ITT population who completed the entire 1-Year Open-Label Period (Visit 1 to Visit 7).

**8. Treatment retention time (time to withdrawal due to lack of efficacy or adverse events).**

If a subject's reason for withdrawal from 1-Year Open-Label Period included: withdrawal of consent, lost to follow-up, physician decision or other, then it will be assumed the subject terminated due to lack of efficacy. For subjects that discontinue due to adverse event or lack of efficacy, the treatment retention time during the 1-Year Open-Label Period will be calculated as the date of last known dose during the 1-Year Open-Label Period minus the date of the first dose of eslicarbazepine acetate monotherapy in protocol 093-045 or 093-046 (Visit 6/Week 8), plus 1. The time may include taking eslicarbazepine acetate concomitantly with other AEDs.

**5.2.3. Post-1-Year Open-Label Period Endpoints**

**1. Patient Global Impression**

PGI measures the effect of study drug by assessing patient overall impression on a 5-point scale from 0 (best score) to 4 (worst score), including:

- Very much improved
- Improved
- No change
- Worse

- Very much worse

PGI will be summarized from Visit 8 every three months during the Post-1-Year Open-Label Period until the End of Study or Early Termination Visit.

## **2 Completion rates**

Completion rates for Post- 1-Year Open-Label Period will be defined as the proportion of subjects from the ITT population who had the reason for withdrawal from the Post- 1 Year Open-Label Period either “Sponsor terminates clinical study” or “Study drug became available in subject’s locale” from the end of study page in the CRF.

## **3. Time on eslicarbazepine acetate monotherapy**

Time on eslicarbazepine acetate monotherapy during Post1-Year Open-Label Period will be calculated from the date of the first eslicarbazepine acetate monotherapy dose in protocol 093-045 or 093-046(Visit 6/Week 8) to the last known dose of eslicarbazepine acetate monotherapy during Post-1-Year Open- Label Period as follows;

- For a subject who added a non-rescue AED during Post-1-Year Open-Label Period, Time on Monotherapy during Post 1-Year Open-Label Period is calculated as the date of start a non-rescue AED during Post-1-Year Open-Label Period minus the date of the first monotherapy dose in protocol 093-045 or 093-046.
- For a subject who completed the Post-1-Year Open-Label Period, and did not add any non-rescue AED since the date of the first monotherapy dose in protocol 093-045 or 093-046, Time on Monotherapy during Post-1-Year Open-Label Period is calculated as the date of the last known dose during Post-1-Year Open-Label Period, minus the date of the first monotherapy dose in protocol 093-045 or 093-046, plus 1.
- For a subject who did not complete the Post-1Year Open-Label Period and did not add any non-rescue AED since the date of the first monotherapy dose in protocol 093-045 or 093-046, Time on Monotherapy during Post- 1-Year Open-Label Period is calculated as the date of the last known dose before the withdrawal during Post- 1-Year Open-Label Period, minus the date of the first monotherapy dose in protocol 093-045 or 093-046, plus 1.

## **4. Treatment retention time**

If a subject’s reason for withdrawal from Post-1-Year Open-Label Period included: withdrawal of consent, lost to follow-up, physician decision or other, then it will be assumed the subject terminated due to lack of efficacy. For subjects that discontinue due to adverse event or lack of efficacy, the treatment retention time during Post-1-Year Open-Label Period will be calculated as the date of last known dose during Post-1-Year Open-Label Period minus the date of the first dose of eslicarbazepine acetate monotherapy in protocol 093-045 or 093-046 (Visit 6/Week 8), plus 1. The time may include taking eslicarbazepine acetate concomitantly with other AEDs.



**5.2.4. Entire Open-Label Period Endpoints**

**1. Change in Quality of Life in Epilepsy**

The QOLIE-31 contains seven multi-item scales that assess the following health concepts: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life. The QOLIE-31 overall score is obtained by using a weighted average of the multi-item scale scores. The QOLIE-31 also includes a single item that assesses overall health on a visual analogue scale. The recorded responses will be converted to 0-100 point scales as described in Table 1. The mean of the individual item scores in each subgroup are then calculated, with higher converted scores reflecting better quality of life. If one item within a scale score is missing, it will be replaced by the mean value of the other items. If more than one item is missing, the scale score will not be calculated.

The QOLIE-31 overall score is obtained by using a weighted average of the 7 scale scores according to the following formula:

$$\begin{aligned} \text{Overall score} &= \text{Seizure worry} * 0.08 \\ &+ \text{Overall quality of life} * 0.14 \\ &+ \text{Emotional well-being} * 0.15 \\ &+ \text{Energy/fatigue} * 0.12 \\ &+ \text{Cognitive functioning} * 0.27 \\ &+ \text{Medication effects} * 0.03 \\ &+ \text{Social functioning} * 0.21 \end{aligned}$$

If no score has been calculated for at least one of the 7 scales, the overall QOLIE-31 score will not be calculated. The change from baseline to each post-treatment assessment in QOLIE-31 overall score will also be calculated.

**Table 1: QOLIE-31 Response Conversions**

Scale	Response						Formula	
	Item Numbers	1	2	3	4	5		6
<b>Seizure Worry</b>								
11.		0	20	40	60	80	100	$((\text{Resp}-1)/(\text{Max}-1))*100$
21.		0	33.3	66.7	100	-	-	$((\text{Resp}-1)/(\text{Max}-1))*100$
22.		0	50	100	-	-	-	$((\text{Resp}-1)/(\text{Max}-1))*100$
23.		0	33.3	66.7	100	-	-	$((\text{Resp}-1)/(\text{Max}-1))*100$



25. 100 75 50 25 0 -  $100 - ((\text{Resp}-1)/(\text{Max}-1)) * 100$

**Overall Quality of Life**

1. Multiply response by 10

14. 100 75 50 25 0 -  $100 - ((\text{Resp}-1)/(\text{Max}-1)) * 100$

**Emotional Well-being**

3. 0 20 40 60 80 100  $((\text{Resp}-1)/(\text{Max}-1)) * 100$

4. 0 20 40 60 80 100  $((\text{Resp}-1)/(\text{Max}-1)) * 100$

5. 100 80 60 40 20 0  $100 - ((\text{Resp}-1)/(\text{Max}-1)) * 100$

7. 0 20 40 60 80 100  $((\text{Resp}-1)/(\text{Max}-1)) * 100$

9. 100 80 60 40 20 0  $100 - ((\text{Resp}-1)/(\text{Max}-1)) * 100$

**Energy/Fatigue**

2. 100 80 60 40 20 0  $100 - ((\text{Resp}-1)/(\text{Max}-1)) * 100$

6. 100 80 60 40 20 0  $100 - ((\text{Resp}-1)/(\text{Max}-1)) * 100$

8. 0 20 40 60 80 100  $((\text{Resp}-1)/(\text{Max}-1)) * 100$

10. 0 20 40 60 80 100  $((\text{Resp}-1)/(\text{Max}-1)) * 100$

**Cognitive Functioning**

12. 0 20 40 60 80 100  $((\text{Resp}-1)/(\text{Max}-1)) * 100$

15. 0 33.3 66.7 100 - -  $((\text{Resp}-1)/(\text{Max}-1)) * 100$

16. 0 20 40 60 80 100  $((\text{Resp}-1)/(\text{Max}-1)) * 100$



17.	0	20	40	60	80	100	$((\text{Resp}-1)/(\text{Max}-1))*100$
18.	0	20	40	60	80	100	$((\text{Resp}-1)/(\text{Max}-1))*100$
26.	100	75	50	25	0	-	$100-((\text{Resp}-1)/(\text{Max}-1))*100$

**Medication Effects**

24.	0	33.3	66.7	100	-	-	$((\text{Resp}-1)/(\text{Max}-1))*100$
29.	100	75	50	25	0	-	$100-((\text{Resp}-1)/(\text{Max}-1))*100$
30.	100	75	50	25	0	-	$100-((\text{Resp}-1)/(\text{Max}-1))*100$

**Social Functioning**

13.	0	20	40	60	80	100	$((\text{Resp}-1)/(\text{Max}-1))*100$
19.	0	25	50	75	100	-	$((\text{Resp}-1)/(\text{Max}-1))*100$
20.	0	25	50	75	100	-	$((\text{Resp}-1)/(\text{Max}-1))*100$
27.	100	75	50	25	0	-	$100-((\text{Resp}-1)/(\text{Max}-1))*100$
28.	100	75	50	25	0	-	$100-((\text{Resp}-1)/(\text{Max}-1))*100$

Resp=Response, Max=Maximum possible response for the respective item.

Change in Quality of Life is defined as the change in QOLIE-31 total score from Visit 2 (Day 0) of Protocols 093-045 or 093-046 to end of study treatment (ET/EOS).

**2. Change in Montgomery-Asberg Depression Rating Scale**

The MADRS measures the effect of study drug on depression severity by assessing the severity of 10 symptoms on a scale from 0 (best score) to 6 (worst score), including:

- Apparent sadness
- Reported sadness
- Inner tension
- Reduced sleep
- Reduced appetite
- Lassitude
- Concentration difficulties
- Suicidal thoughts
- Inability to feel
- Pessimistic thoughts

The total score is defined as the sum of all individual item scores. If one item is missing at a given visit, it will be replaced with the mean of the answers that are present. If more than one item is missing at a given visit, no total score will be calculated.

Change in MADRS total score will be summarized from Visit 2 (Day 0) of Protocols 093-045 or 093-046 (baseline) to end of study treatment (ET/EOS). This analysis will be repeated for subjects with a MADRS score of  $\geq 14$  at screening visit (Visit 1) of the present study.

### 5.3. Safety Assessments and Endpoints

#### 5.3.1. Safety Assessments

Adverse events will be monitored throughout the study, starting at Visit 1.

Clinical laboratory tests to be collected include: serum chemistry, hematology, thyroid panel (free T3, free T4, and TSH), coagulation testing (prothrombin time [PT]/international normalized ration [INR] and partial thromboplastin time [PTT]), lipid panel (total cholesterol, high-density lipoprotein [HDL]-cholesterol, low-density lipoprotein [LDL]-cholesterol, and triglycerides), 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]), and urinalysis.

A 12-lead ECG collect ventricular heart rate, QT interval, P-R interval, QRS durations, R-R interval, and the QTc intervals corrected by Bazett (QTcB) and Fridericia (QTcF).

Vital signs include standing and supine systolic and diastolic blood pressure, standing and supine heart rate, respiration rate, weight, and body temperature.

Physical and neurological examinations will be conducted at Visit 1 and the End of Study or Early Termination Visit.



The C-SSRS is an instrument designed to systematically assess and track suicidal events (suicidal behavior and suicidal ideation) throughout the study. The C-SSRS includes the following four sections: Suicidal Ideation, Intensity of Ideation, Suicidal Behavior and Actual Suicide Attempts. The C-SSRS will be completed by the Investigator or Sub-Investigator (or qualified site personnel).

### 5.3.2. Safety Endpoints

#### Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 13.1.

Treatment-emergent adverse events (TEAEs) will be defined as:

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

Adverse events whose relationship is assessed as “not related” will be grouped as “unrelated.” Otherwise, adverse events assessed as “unlikely,” “possible,” “probable,” or “definite,” unknown or missing will be grouped as “potentially related.” Further, if a subject reports more than one AE within the same treatment regimen, system organ class (SOC) and preferred term (PT), and any are related, it will be summarized as related.

If a subject has more than one occurrence of an event within a SOC and/or PT, the subject incidence summaries will count each subject only once within that SOC and/or PT. In the case of more than one event within a SOC and/or PT, the event with the highest severity will be summarized in the by-severity summaries and the one with the strongest relationship will be summarized in the by-relationship summaries.

TEAEs will be sorted by SOC in alphabetical order and then by PT sorted by decreasing frequency, with preferred terms with the same frequency sorted in alphabetical order.

#### Clinical Laboratory Evaluation

Observed values and change from baseline will be summarized for each visit, where change from baseline is the result of interest minus baseline value (Visit 2/Day 0 from protocol 093-045 or 093-046).

Each laboratory result will be cross referenced with laboratory-provided normal reference ranges to determine whether the test result is below, within, or above the normal range. Similarly, sponsor defined-potentially clinically significant (PCS) laboratory results will be identified using the criteria in Table 2.

Additionally, the number and percent of the subjects with normal baseline (Visit 2/Day 0 from protocol 093-045 or 093-046) sodium levels reaching the following post-baseline blood sodium levels as below categories will be identified by time point:

- $\leq 135$  mEq/L and  $> 130$  mEq/L
- $\leq 130$  mEq/L and  $> 125$  mEq/L
- $\leq 125$  mEq/L
- $> 10$  mEq/L reduction (i.e.  $< -10$  mEq/L) from baseline

**Table 2: PCS Criteria for Laboratory Parameters**

Parameter Name	PCS Low	PCS High
<b>Hematology</b>		
WBC	$\leq 2.8 \times 10^9/L$	$\geq 16 \times 10^9/L$
Neutrophils	$< 1.5 \times 10^9/L$	$> 13.5 \times 10^9/L$
Lymphocytes	N/A	$> 12 \times 10^9/L$
Monocytes	N/A	$> 2.5 \times 10^9/L$
Eosinophils	N/A	$> 1.6 \text{ k/mm}^3$
Basophils	N/A	$> 1.6 \text{ k/mm}^3$
Hemoglobin for Females	$\leq 9.5 \text{ g/dL}$	$\geq 17.5 \text{ g/dL}$
Hemoglobin for Males	$\leq 11.5 \text{ g/dL}$	$\geq 19.0 \text{ g/dL}$
Hematocrit for Females	$\leq 32\%$	$\geq 54\%$
Hematocrit for Males	$\leq 37\%$	$\geq 60\%$
RBC	$\leq 3.5 \times 10^{12}/L$	$\geq 6.4 \times 10^{12}/L$
Platelet Count	$\leq 75 \times 10^9/L$	$\geq 700 \times 10^9/L$
<b>Chemistry</b>		
Sodium	$\leq 126 \text{ mEq/L}$	$\geq 156 \text{ mEq/L}$
Potassium	$\leq 3 \text{ mEq/L}$	$\geq 6 \text{ mEq/L}$
Chloride	$\leq 90 \text{ mEq/L}$	$\geq 118 \text{ mEq/L}$
Calcium	$< 8.2 \text{ mg/dL}$	$\geq 12 \text{ mg/dL}$
AST	N/A	$\geq 3 \times \text{ULN}$
ALT	N/A	$\geq 3 \times \text{ULN}$
Alkaline phosphatase	N/A	$\geq 3 \times \text{ULN}$
Creatinine	N/A	$\geq 2 \text{ mg/dL}$
BUN	N/A	$\geq 30 \text{ mg/dL}$
Total bilirubin	N/A	$\geq 2 \text{ mg/dL}$
Total protein	$\leq 4.5 \text{ g/dL}$	$\geq 10 \text{ g/dL}$
Albumin	$\leq 2.5 \text{ g/dL}$	N/A
Glucose	$\leq 40 \text{ mg/dL}$	$\geq 175 \text{ mg/dL}$
Creatinine Phosphokinase	N/A	$> 2.5 \times \text{ULN}$

Phosphate	< 2.0 mg/dL	> 5.3 mg/dL
HDL-Cholesterol	< 30 mg/dL	N/A
LDL-Cholesterol	N/A	> 160 mg/dL
Total Cholesterol	> 300 mg/dL	N/A
Triglycerides	N/A	> 2.5 x ULN
<b>Blood Coagulation</b>		
aPTT	N/A	> 1.5 ULN
INR	N/A	> 1.5 ULN
<b>Thyroid Function</b>		
Free T3	< 0.20 ng/dL	> 0.415 ng/dL
Free T4	< 0.75 ng/dL	> 1.75 ng/dL

### 12-Lead ECG

Observed values and change from baseline will be summarized for each visit, where change from baseline is the result of interest minus the baseline result (Visit 2 from protocol 093-045 or 093-046).

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

- QTc-F >500 ms at any postdose time point not present at baseline
- QTc-F >480 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 incidence of specific ECG abnormalities will also be identified for the following categories:

- Overall abnormalities
- Rhythm abnormalities
- Conduction abnormalities
- Morphology abnormalities
- Myocardial infarction
- Presence of ST Segment abnormalities
- Presence of T wave abnormalities
- Presence of U wave abnormalities

### Vital Signs

Observed values and change from baseline will be summarized for each visit, where change from baseline is the result of interest minus the baseline result (Visit 2 from protocol 093-045 or 093-046).

In addition, subjects meeting the sponsor defined vital sign PCS criteria (Table 3) will be identified.

A vital sign value is considered PCS low if it is below the specified low limit and it decreases from baseline more than the specified decrease from baseline limit. A vital sign value is considered PCS high if it is higher than the specified high limit and it increases from baseline more than the specified increase from baseline limit.

**Table 3: PCS Criteria for Vital Signs**

Parameter Name	Low	Decrease from Baseline	High	Increase from Baseline
Supine Systolic BP	< 90 mm Hg	≥ 20 mm Hg	> 180 mm Hg	≥ 20 mm Hg
Supine Diastolic BP	< 50 mm Hg	≥ 15 mm Hg	> 105 mm Hg	≥ 15 mm Hg
Supine Heart Rate	< 50 bpm	≥ 15 bpm	> 120 bpm	≥ 25 bpm
Weight	N/A	≥ 7%	N/A	≥ 7%

### Body Weights

Observed weight values and change from baseline will be summarized for each visit, where change from baseline is the weight at the visit of interest minus the baseline weight (Visit 2 from protocol 093-045 or 093-046). Subjects with a weight change of ≥7% will be identified at each visit by dividing the change from baseline weight, by the baseline weight, and multiplying by 100.

### Orthostatic Effects

The number and percentage of subjects who experienced orthostatic hypotension and orthostatic tachycardia will be summarized. Orthostatic effects can be determined for a vital sign, by examining the difference between positions.

(Standing result during the interval of interest)- (Supine result during the interval of interest)

Orthostatic hypotension is having a difference of ≤ -20 mmHg in systolic or ≤ -10 mmHg in diastolic blood pressure. Orthostatic tachycardia will be defined as a difference in heart rate ≥ 20 beats per minute and the standing heart rate >100 beats per minute after the subject was standing for at least 2-4 minutes.

### Other Safety Assessments

Physical and neurological examinations performed at Visit 1 of protocols 093-045 or 093-046 will apply to Visits 1 (Screening) of the present study.

### Columbia-Suicide Severity Rating Scale (C-SSRS)

Occurrence of suicidal ideation is defined as having answered “yes” to at least one of the 5 suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act,

active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) at any evaluation. Occurrence of suicidal behavior is defined as having answered “yes” to at least one of the 4 suicidal behavior sub-categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior) at any post baseline evaluation. Suicidal ideation is rated on a 6-point scale from 0=’No ideation present’ to 5=’Active ideation with plan and intent’. A score of 4 or 5 on this scale indicates serious suicidal ideation.

Suicidality is defined as having at least one occurrence of suicidal ideation or at least one occurrence of suicidal behavior during the assessment period.

### **Concomitant medications**

All medications will be coded using WHO Drug, version 01Jun2009. The number and percentage of subjects using each concomitant medication will be summarized according to the WHO DRUG Class and preferred term (PT). Subjects with multiple uses of a concomitant medication will be counted once for a given WHO Drug Class and PT. Prior medications are defined as any medication with an end date before the first dose of study medication. Concomitant medications are defined as medications present on or after the first dose of study medication.

## **6. Statistical Methods**

### **6.1 General Methodology**

All statistical procedures will be performed using SAS Version 9.2 or higher.

Continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics, including the number of subjects, mean, standard deviation, minimum, 25<sup>th</sup> percentile, median, 75<sup>th</sup> percentile, and maximum. For categorical variables, summaries will include counts of subjects and percentages.

### **Baseline**

Change in seizure related efficacy parameters will be calculated with reference to the baseline period defined as the baseline period (From Visit 1 to Visit 2) from protocol 093-045 and 093-046. The change in QOLIE, MADRS and safety parameters will be calculated with reference to the baseline as Day 0 (Visit 2) for protocol 093-045 and 093-046.

### **3-month visit windows**

There are four 3-month intervals for the 1-Year Open-Label Period. The first window is defined as  $\geq$ Visit 1 and  $<$ Visit 4, the second window is  $\geq$ Visit 4 and  $<$ Visit 5, the third window is  $\geq$ Visit 5 and  $<$ Visit 6 and the fourth window is  $\geq$ Visit 6 and  $<$ Visit 7). This 3-month interval will be used to summarize seizure related efficacy data.

### **6.2 Handling of Dropouts or Missing Data**

Subjects who dropped out before study completion are not to be replaced and all available information obtained from them will be included in the appropriate efficacy



and safety summaries to the time of dropout. No imputation is planned for any safety measures.

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

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

For QOLIE31 and MADRS, if only one item is missing, it will be imputed by the average of other items for calculating the total score (See Section 5.2.4: 1 and 2).

### **6.3 Interim Analyses and Data Monitoring**

There will be no interim analysis or formal data monitoring during this study.

### **6.4 Multiple Comparisons/Multiplicity**

There will be no multiple comparison/multiplicity for this study.

### **6.5 Examination of Subgroups**

To examine potential differences in the outcomes by the subgroups as below, the following data will be summarized separately by the subgroups: SSF, Relative change (%) from baseline in SSF, responders, adverse events, and PCS laboratory parameters.

#### **Demographic subgroups**

- Age (<18, 18-65, >65 years old)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, Other)

#### **Baseline AEDs subgroups**

An AED is considered to be used at baseline if it started at any time prior to the first dose of study treatment and continued into the titration period from protocol 093-045 or 093-045. Subjects may appear in multiple AED use subgroups.

- Number of baseline AEDs (0, 1, 2, or more AEDs)
- Baseline AEDs
  - Use of carbamazepine as baseline AED (yes/no)
  - Use of oxcarbazepine as baseline AED (yes/no)
  - Use of carbamazepine or oxcarbazepine as baseline AED (yes/no)
  - Use of lamotrigine as baseline AED (yes/no)

- Additional individual baseline AEDs that occur in  $\geq 15\%$  of the subjects (namely, levetiracetam, and valproic acid)

### **Seizure subgroups**

Seizure type (simple partial, complex partial, partial evolving to secondarily generalized seizures)

### **Actual Monotherapy Used subgroup**

The subjects who started on actual monotherapy (i.e. 10 weeks double-blind monotherapy from protocol 093-045 or 093-046), entered this study and did not add any non-rescue AED during the study participation will be defined as Actual Monotherapy Used subgroup.

For those subjects, the following data including ESL exposure and compliance, concomitant medication, SSF, relative (%) change from baseline in SSF, responders, TEAE, SAE, Death, TEAE leading to discontinuation, and minimum post-dose sodium level change from baseline will be summarized.

## **7. Statistical Analysis**

### **7.1 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 all safety and all efficacy analyses.

The per-protocol (PP) population will consist of all subjects in the ITT population who did not have any important protocol deviations. The per-protocol population will be used in an additional analysis of the efficacy endpoints and subject demographics and baseline characteristics.

### **7.2 Disposition of Subjects**

The number and percentage of subjects who entered 1-Year Open-Label Period, who completed the 1-Year Open-Label Period, who discontinued during 1-year Open-Label Period (including reasons for discontinuations), who completed 1-Year Open-Label period but did not enter the Post-1-Year Open-Label Period, entered Post-1-Year Open-Label Period, and discontinued early (including reasons for discontinuations) for Post-1-Year Open-Label Period, and who completed Post-1-Year Open-Label Period will be summarized. The number and percentage of subjects who were in actual monotherapy used subgroup and PP population will be also summarized respectively.

Subject disposition will be summarized for the ITT population.

Listing of subject disposition will be provided.

### 7.3 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 (e.g., inclusion/exclusion criteria violations) or through review of data listings (e.g., 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.

Listing of IPDs will be provided. In addition, subject inclusion and exclusion criteria will be provided.

### 7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics at Screening/Visit 1 from Protocol 093-045 or 093-046 will be summarized including age, gender, race, ethnicity, country, height, weight, and BMI (continuous and categorized as <18, 18-30, >30 kg/m<sup>2</sup>), concomitant AEDs, country, region (US/Non-US), as well as disease conditions, will be summarized using descriptive statistics.

Demographic and baseline characteristics, Medical history, and Epilepsy history will be summarized for the ITT population.

Listing of demographic and baseline characteristic data, medical history, and epilepsy history will be provided.

### 7.5 Extent of Exposure and Compliance

The extent of exposure will be summarized descriptively: it will be calculated as the date of last reported dose minus the first dose date of 093-050 study, ignoring missing days plus 1. If the day of first dose of study drug is unknown, this will be set to the first dispensing date. If the day of last dose of study drug is unknown, then this will be set to the day of last contact.

Extent of exposure will be summarized by the following mean daily dose categories:

- ESL < 1000 mg
- ESL 1000 mg – <1400 mg

- ESL 1400 mg – <2000 mg
- ESL  $\geq$  2000 mg
- Total ESL

**Duration of Exposure:**

The frequency of duration of exposure will be summarized using the following categories:

- 1-7 Days
- > 1-2 Weeks
- > 2-4 Weeks
- > 4-6 Weeks
- > 6-8 Weeks
- > 8-10 Weeks
- >10-12 Weeks
- > 12-14 Weeks
- > 14-16 Weeks
- > 16-18 Weeks
- > 18-20 Weeks
- > 20-26 Weeks
- > 26-52 Weeks
- > 52-104 Weeks
- > 104 Weeks (24 Months)

Subject-years of exposure will be calculated by summing the overall exposure for each subject within the dose group dividing by 365.25.

The number of tablets taken per subject will be summarized as a continuous variable. The total number of tablets taken will be determined by subtracting the total number of tablets returned and reported lost from the total number of tablets dispensed.

Continuous summaries of mean daily dose will also be presented. The mean daily dose level (mg) of ESL will be calculated as the total number of tablets taken within each treatment interval multiplied by the tablet strength, and then divided by the duration (in days) of treatment within the treatment interval. The overall mean daily dose will be calculated as the weighted average of the treatment intervals (i.e., the sum of the non-missing mean daily doses for each treatment interval multiplied by their respective number of days in the interval, divided by the total number of days in the

intervals with non-missing mean daily doses).

Descriptive statistics will be used to summarize percent compliance. Further, the number and percent of subjects that are <80%, 80-120% or >120% will be displayed.

Percent compliance will be derived as the number of tablets taken divided by the number of tablets that should have been taken, expressed as a percent.

Listing of subject treatment exposure and compliance will be provided. In addition, listing of study drug dosing and study drug accountability including number of tablets dispensed, returned, lost/missing, taken will be provided.

## 7.6 Efficacy Analyses

ITT population will be used for all the efficacy analyses. For the analysis of seizure data, listing of seizure symptoms, seizure diary, and SSF and related derived parameters will be provided.

### **Time on eslicarbazepine acetate monotherapy**

Kaplan Meier methods will be used to estimate the median time (and 95% CI) on eslicarbazepine acetate monotherapy for both 1-Year Open-Label Period and Post-1-Year Open-Label Period.

For the 1-Year Open-Label Period, time on monotherapy as defined in Section 5.2.2 will be used for analysis. Subjects who were still taking only eslicarbazepine acetate as monotherapy at the end of the 1-Year Open-Label Period of study will be censored at the last dose of the 1-Year Open-Label Period. Subjects who withdrew during the 1-Year Open-Label Period will also be censored at the time of the last known dose before the withdrawal. Subject who added a non-rescue AED will be an event on the date of the start AED during 1-Year Open-Label Period.

For the Post-1-Year Open-Label Period, time on monotherapy as defined in Section 5.2.3 will be used for analysis. Subjects who were still taking only eslicarbazepine acetate as monotherapy at the end of the Post-1-Year Open-Label Period will be censored at the last dose of the Post-1-Year Open-Label Period. Subjects who withdrew during the Post-1-Year Open-Label Period will also be censored at the time of the last known dose before the withdrawal. Subject who added a non-rescue AED will be an event on the date of the start AED during Post-1-Year Open-Label Period.

Subjects who never started the monotherapy treatment period in protocol 093-045 or 093-046 will not be included in this analysis. Change in dosage levels from protocol 093-045 or 093-046, dosage changes during protocol 093-050, and the time gap between the parent studies and the extension study will be ignored.

### **Seizure standard frequency (SSF)**

Descriptive statistics will summarize the SSF for 1 week, 1 month, each 3 month visit window of time, overall, and by the following subgroups: number of baseline AEDs,

and baseline AED medications, and seizure type.

**Relative (%) change from baseline in SSF**

Relative (%) change from baseline in SSF will be summarized descriptively for 1 week, 1 month, each 3-month visit window, overall, and by the following subgroups: number of baseline AEDs, and baseline AED medications, seizure type. The number and percentage of subjects with the category in Section 5.2.2 will also be presented.

**Responder rate**

The number and proportion (%) of responders with 95% confidence intervals (using binomial methods) will be presented for 1 week, 1 month, each 3-month visit window, overall, and by the following subgroups: number of baseline AEDs, and baseline AED medications.

**Seizure-free**

The number and proportion (%) of subjects that are seizure-free with 95% confidence intervals (using binomial methods) will be presented for 1 week, 1 month, each 3-month visit window and overall.

**Completion rate**

The number and proportion (%) of subjects completing the 1-Year Open-Label Period and Post-1-Year Open-Label Period will be provided along with a 95% confidence interval (using binomial methods).

**Treatment retention**

Kaplan Meier methods will be used to estimate the median retention time (and 95% CI) on eslicarbazepine acetate for subjects who discontinued early due to adverse event(s) or lack of efficacy for both 1-Year Open-Label Period and Post-1-Year Open-Label Period.

For 1-Year Open-Label Period, subjects who discontinued the study not due to those reasons (i.e. protocol deviation) as defined in Section 5.2.2 will be censored at the date of the last known dose during 1-Year Open-Label Period. Subjects who were still taking eslicarbazepine acetate at the end of the 1-Year Open-Label Period of study will be censored at the last dose of the 1-Year Open-Label Period.

For Post-1-Year Open-Label Period, subjects who discontinued the study not due to those reasons (i.e. protocol deviation, study drug became available in subject's locale, and sponsor terminates clinical study) as defined in Section 5.2.3 will be censored at the date of the last known dose during Post-1-Year Open-Label Period. Subjects who were still taking eslicarbazepine acetate at the end of the Post-1-Year Open-Label Period of study will be censored at the last dose of the Post-1-Year Open-Label Period.

### **Change in Quality of Life in Epilepsy (QOLIE-31)**

Values and change from baseline (Visit 2, Day 0 from protocol 093-045 or 093-046) in the seven individual items, overall score, and global assessment will be summarized with descriptive statistics for each visit. A listing of subjects with QOLIE-31 assessments will be provided.

### **Change in Montgomery-Asberg Depression Rating Scale (MADRS)**

The total MADRS score and the 10 individual items will be summarized descriptively for each evaluation visit, along with the change from baseline (Visit 2, Day 0 from protocol 093-045 or 093-046).

In addition, this analysis will be repeated for those subjects with a MADRS score of  $\geq 14$  at screening (Visit 1) of this study. A listing of subjects with MADRS assessments will be provided.

### **Patient Global Impression (PGI)**

The total PGI score and the 5 individual items will be summarized descriptively from Visit 8 every three months during the Post-1-Year Open-Label Period, until the End of Study or Early Termination Visit.

Listing of Patient Global Impression (PGI) will be provided.

## **7.7 Safety Analyses**

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.

### **7.7.1 Adverse Events**

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

- All AEs (including number of events and subject incidence)
- AEs by severity (mild, moderate, severe)
- All serious adverse events (SAE)
- All AEs by relationship to treatment (unrelated, or potentially related)
- AEs leading to death
- AEs leading to discontinuation

All above AEs and the AE subgroup analyses in Section 6.5 will be summarized for the three periods as below.

- Year Open-Label Period
- Post-1-Year Open-Label Period
- Combined 1-Year Open-Label Period and Post-1-Year Open-Label Period



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

### 7.7.2 Clinical Laboratory Evaluation

Descriptive statistics for test results and change from baseline (Visit 2/Day 0 from protocol 093-045 or 093-046) will be displayed at each scheduled visit (i.e. Visit 3-Visit 7) for each continuous laboratory parameter.

The normal reference ranges for laboratory tests will be used to determine whether the laboratory test value is below, within, or above the normal range. Shifts from baseline to each visit will be produced to show the percentage of subjects with laboratory test values below, within, and above the normal range. The percentage will be based on the number of subjects with a baseline result and at least one post-baseline result for each parameter.

Clinical significance of post-baseline abnormally low and high values will be summarized for each lab parameters.

A listing of urine drug screen and serum pregnancy test results will also be provided.

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 PCS criteria will be summarized by overall, and by the subgroups including age group, race, gender, number of baseline AED and baseline AEDs.

The listing of the Special Interest of Elevation defined as elevation of any post-dose AST or ALT > 3x ULN will be provided.

Listing of clinical laboratory measurements (hematology, serum chemistry, urinalysis, blood coagulation, bone turnover marker measurements) will be provided.

In addition, listing of clinically significant out of range laboratory measurements, laboratory comments, and listing of subjects meeting any of the PCS lab criteria will be provided.

In addition to continuous summaries of blood sodium levels, the number and percentage of subjects with normal baseline sodium level and a post-baseline level  $\leq 135$  mEq /L but  $> 130$  mEq /L,  $\leq 130$  mEq /L but  $> 125$  mEq /L,  $\leq 125$  mEq /L, and  $> 10$  mEq/L reduction (i.e.  $< -10$  mEq/L) from baseline will be summarized by time point and overall post-baseline.

Above blood sodium levels will be also summarized by baseline AED and for actual monotherapy used subgroup.

### 7.7.3 ECG Evaluations

Descriptive statistics for each parameter and change from baseline (from protocol 093-045 or 093-046) values will be displayed at each scheduled visit (i.e. Visit 3-Visit 7) for each ECG parameter.





The number and percentage of subjects with QTc-F values in the categories as defined in Section 5.3.2 will be summarized.

- QTc-F >500 ms at any post-baseline time point not present at baseline
- QTcF >480 ms at any post-baseline timepoint not present at baseline
- QTc-F >450 ms at any post-baseline time point not present at baseline
- Change from baseline in QTc-F  $\geq$ 60 ms for at least 1 post-baseline measurement
- Change from baseline in QTc-F  $\geq$ 30 ms for at least 1 post-baseline measurement, but <60 ms for all post-baseline 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.

Listing of 12-Lead ECG Measurements, Abnormality Findings and Overall Interpretation, and 12-Lead ECG collections will be provided.

#### **7.7.4 Vital Signs**

Observed values and change from baseline period (Visit 1-2 in 093-045 or 093-046) in each vital sign parameter will be summarized at baseline and by visit. A listing of vital signs will be provided. Height will only be summarized at baseline and end of study.

In addition, the number and percentage of subjects meeting sponsor defined PCS vital sign values (outlined in Table 3) will be summarized for 1-Year Open-Label Period and Post-1-Year Open-Label Period.

In addition a listing of subjects meeting any of the PCS vital signs criteria defined by the sponsor will be provided.

#### **7.7.5 Orthostatic Effects**

The number and percentage of subjects who had orthostatic effects (hypertension and tachycardia in Section 5.3.2) will be summarized from Visit 1 (Day 0) until the End of Study or Early Termination Visit for the ITT population.

#### **7.7.6 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.) for the ITT population.

Listing of physical examination findings and neurological examination findings will be provided.

#### **7.7.7 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 WHO Drug Class and preferred term for concomitant AED and non-AED medication separately. Subjects with multiple uses of a concomitant medication will be counted once for a given WHO Drug Class and Preferred term.

Listing of concomitant AED, non-AED medications, prior medication, and rescue and emergency medication will also be presented.

#### **7.7.8 Columbia-Suicide Severity Rating Scale (C-SSRS)**

Results from the C-SSRS assessments will be summarized by presenting the number and percentage of subjects with any suicidality, suicidal behavior and type of behavior, and any suicidal ideation and type of ideation.

Shifts in suicidal ideation from baseline to worst post-baseline result will be presented. Worsening ideation is reflected in shifts from lower to higher values.

C-SSRS will be summarized from Visit 1 until the End of Study or Early Termination Visit for the ITT population.

Listing of the C-SSRS assessments will also be presented.

### **8. References**

- 1 Cramer, JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann BP. Development and cross-cultural translation of a 31-item quality of life questionnaire (QOLIE-31). *Epilepsia*. 1998; 39:81-88.
2. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979; 134:382-389.