Double-Blind, Randomized, Two Period Crossover Comparison of the Cognitive and Behavioral Effects of Eslicarbazepine Acetate and Carbamazepine in Healthy Adults

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TITLE: Double-Blind, Randomized, Two Period Crossover Comparison of the Cognitive and Behavioral Effects of Eslicarbazepine Acetate and Carbamazepine in Healthy Adults

BRIEF DESCRIPTION OF STUDY

This study is a double-blind, randomized, two period crossover design. The study consists of 6 visits over a 21 week period. Fifty (50) normal healthy subjects will be treated with both Eslicarbazepine acetate (ESL, 800 mg/day) and Carbamazepine (CBZ, 800mg/day) for 6 weeks and 3 days each (maintenance 4 weeks and taper 3 days). Each antiepileptic drug (AED) treatment period will be followed by a four day taper and washout period off AED for the remainder of the month. Cognitive and behavioral function testing along with safety testing will be conducted at pretreatment baseline, the end of each randomization AED maintenance period, and after the final washout period.

TIME PERIOD AND NUMBER OF SUBJECTS

A. Anticipated Number of Subjects: 50 (to obtain 30 evaluable subjects)
B. Anticipated Duration of Study: 1 Year

DESCRIPTION OF MEDICATIONS

Generic	Strength and Dosage Form	Therapeutic Classification
ESL	400 mg/capsule	Anticonvulsant
CBZ (immediate release)	200 mg/capsule	Anticonvulsant

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I. BACKGROUND AND RATIONALE

The efficacy of antiepileptic drugs (AEDs) in reducing seizures is similar for the most common type of seizures (i.e., focal +/- secondary generalized). Therefore, differential side effects play an important role in therapeutic decisions. In this regard, differential cognitive effects of AEDs are of particular interest. The older AEDs are known to produce untoward cognitive effects, which are clinically significant in some patients (Meador, 2001a). The cognitive effects of carbamazepine, phenytoin, and valproate are similar while the effects of phenobarbital are worse. Several of the newer AEDs are well tolerated and demonstrate fewer adverse cognitive effects compared to placebo and to older AEDs (Meador, 2014a, 2014b).

Eslicarbazepine acetate (ESL) is a new generation AED, which is chemically related to carbamazepine and oxcarbazepine, but is structurally different at the 10,11-position, which results in differences in metabolism. ESL is rapidly hydrolyzed to eslicarbazepine. Eslicarbazepine's main mechanism is blockade of voltage-gated sodium channels, but it also affects type T calcium channels (Hebeisen et al., 2011; Brady et al., 2011). There have been 3 phase III clinical trials: (Elger et al., 2009; Ben-Menachem et al., 2010; Sperling 2015), all with similar design in which ESL was titrated over 2 weeks and then administered for 12 weeks at 400 mg (not in one trial), 800 mg and 1.200 mg once-daily. ESL demonstrated good efficacy in adjunctive therapy for partial seizures with and without secondary generalization. However, ESL's cognitive effects in relation to the established AEDs are unknown.

Only one study has formally assessed the cognitive effects of ESL (Milovan et al, 2010). This investigation consisted of two single-blind parallel-group studies. In the first study, a single dose of 900mg of either ESL or Oxcarbazepine. This was followed by one week of placebo, then one week of ESL 800mg daily or Oxcarbazepine 300mg bid, then one week of ESL 1200mg daily or Oxcarbazepine 600mg bid. Cognitive testing was conducted pre and 3 hours post the single dose and one hour post dose at the end of each week. The total n = 56 healthy subjects with ESL (n=26) and Oxcarbazepine (n=30). The overall treatment-emergent adverse effects (especially CNS related) were greater for Oxcarbazepine. At the top doses, Oxcarbazepine had 83% of patients reporting adverse events compared to 30% for ESL; the CNS adverse reports for asthenia, dizziness, somnolence and blurred vision were greater for Oxcarbazepine. In contrast, differences between ESL and Oxcarbazepine on the cognitive measures were not significant. This disparity may be related to weaknesses in the study design. Weaknesses included small sample size, short duration of therapy, and lack of control for repeated testing (placebo tested only after the first week). The sample size was 56 (26 ESL; 30 oxcarbazepine) which may be too small to detect differences in a parallel design study; the sample size was not determined by statistical considerations. In addition, primary comparisons were for each AED to the predose in the first single dose phase "or" to the placebo phase. Direct comparisons between AEDs were done as secondary analyses. Further, the testing was conducted one hour after the morning dose of the two AEDs (e.g., ESL 1200mg and Oxcarbazepine 600mg), even though ESL would be more likely to be given qHS in the real world. This biased against ESL. Thus, this investigation does not adequately assess the cognitive effects of ESL.

The present study will investigate the cognitive and behavioral effects of ESL

compared to Carbamazepine in healthy subjects employing a double-blind, two-period, crossover design. The design provides robust statistical strength and controls for selection bias created by individual variability in cognitive performance. The use of healthy subjects will control for the effect of changes in seizure frequency on cognitive function. In addition, examining AED cognitive effects in healthy subjects allows extrapolation of the results to other patient populations treated with AEDs (e.g., psychiatric and pain disorders).

II. STUDY QUESTION

What are the cognitive and behavioral effects of ESL compared to Carbamazepine in normal healthy adults?

III. STUDY OBJECTIVE

The objective of this study is to determine whether there are any differences in the cognitive abilities and/or behavioral response of normal healthy volunteers after 6 weeks of treatment with ESL compared to Carbamazepine.

IV. STUDY DESIGN

The study will employ a double-blind, randomized, two period crossover design. Every subject will receive each AED for 6 weeks and 3 days, which includes a one-month maintenance period and 3 day taper. Following neuropsychological assessment at the end of the maintenance phase, AEDs will be tapered off over 3 days and then the subjects will remain off drug for the remainder of 4 weeks. A study physician will monitor each subject during AED treatment periods and will adjust AED dosages with the goal of reaching therapeutic doses of ESL (800mg/day) and Carbamazepine (800mg/day). Subjects will undergo cognitive and behavioral testing at screening, prior to initiation of the first AED, at the end of each AED treatment, and at the end of each of the two washout periods. Subjects and study personnel in direct contact with subjects will be blinded to AED treatment.

V. STUDY POPULATION

A. Number and type of subjects

Healthy males and females between the ages of 18 and 55 who do not require concomitant medications that affect study medications or cognitive and behavioral functions. Fifty subjects will be enrolled in the study in order to complete 30 subjects.

B. Inclusion Criteria

1. Healthy adults between the ages of 18 and 55 years

2. Male or female (using approved birth control methods)

3. Informed consent obtained

C. Exclusion Criteria

1. Presence of clinically significant cardiovascular, endocrine, hematopoietic, hepatic, neurologic, psychiatric, or renal disease.

2. Presence or history of drug or alcohol abuse.

3. The use of concomitant medications, which are known to affect ESL or Carbamazepine or the use of any concomitant medications that may alter cognitive function (see Section VII.E for a partial list).

4. Prior adverse reaction to or prior hypersensitivity to either study medication or to related compounds.

5. Prior participation in studies involving anticonvulsant medications.

6. Subjects who have received any investigational drug within the previous thirty days.

7. Subjects with IQ $\leq$ 70 as determined by the Peabody Picture Vocabulary Test.

8. Presence of HLA B*1502 in subjects of Asian descent; this will be obtained at screening in subjects of Asian descent.

VI. STUDY PROCEDURES

A. Overview: time and events

The study will employ a double-blind, randomized, two-period crossover design. The study consists of 6 visits over a 21 week time period. Subjects will be screened and tested at baseline, and then randomly assigned to receive each AED for 6 weeks, which includes a titration period and a one-month maintenance period. Each AED treatment period will be followed by a 3-day taper and a washout period for the remainder of 4 weeks. (See Appendix A for a complete study timetable).

B. Blinding and Controls

Subjects and study personnel will be blinded to drug randomization since all study drugs will be over-encapsulated in identical capsules.

C. Dosage Regimen

During each AED phase, subjects will be titrated onto ESL (800mg/day) or

Carbamazepine (400mg bid) and tapered off at end of 4-week maintenance according to the following schedule during each treatment arm:

Week	ESL	Carbamazepine
1	400 mg qAM + placebo	200 mg bid
2	400 mg qAM + placebo	200 mg qAM & 400mg qHS
3	800 mg qAM + placebo	400 mg bid
4	800 mg qAM + placebo	400 mg bid
5	800 mg qAM + placebo	400 mg bid
6	800 mg qAM + placebo	400 mg bid
3-day taper	400 mg qAM + placebo	200 mg bid
Stop		

The investigative team will monitor each subject's progress and safety during AED treatment periods with the goal of obtaining and maintaining ESL and Carbamazepine at dosage of 800mg/day. Subjects will remain on each AED for a total of 6 weeks (4 weeks maintenance), and then will be tapered off over 3 days followed by washout period for the remainder of 4 weeks. Total time on each drug will be 6 weeks plus 3 days. ESL will be dosed qAM and Carbamazepine will be dosed BID. The plasma T_{max} for plasma eslicarbazepine and carbamazepine will therefore approximately match the time of testing. Subjects will be tapered off AEDs over the first 3 days of each 4-week washout period according to the following schedules:

AED Dose DURING TRIAL	AED TAPER
ESL = 800	400mg daily X3 days then stop
Carbamazepine = 800	200mg bid X3 days then stop

An appropriate number of placebo capsules will be added to all AED dosages so that subjects will always take the same number of capsules for each dose given BID during AED treatment periods. Dosage times will be 8am and 8pm.

D. Enrollment Goals

Previous studies indicate that an enrollment of 46 subjects will be required to obtain 30 evaluable subjects. See Statistical Section for power analysis.

E. Visit-Specific Treatment and Evaluation Sequence

Subjects will be randomly assigned to receive both AEDs, for 6 weeks each, in a random sequence of administration. Each AED treatment period will be followed by a 3-day taper period and a 25-day washout period.

At all visits, subjects will be advised on drug compliance and avoidance of medications which my adversely effect the results of cognitive function testing. Adverse events will be documented on the appropriate case report form. Appointments will be made for follow up

visits and care will be taken to schedule all cognitive and behavioral function testing for a given subject at the same time of the day. Testing will be in the approximately 2 hours post morning dose. The time of testing and time of last 2 doses will be recorded.

The timetable for the study is listed in Appendix A. This is a visit-by-visit description of the events scheduled for each visit.

Visit 1 Screening Visit (-1 week prior to randomization)

Subjects will be screened to assure they meet all of the inclusion criteria and none of the exclusion criteria. All eligible subjects will be required to give informed consent. A complete history, physical examination, neurologic examination, laboratory screening including urine pregnancy test (if woman of child bearing potential), HLA B*1502 testing for subjects of Asian descent, IQ screen with Peabody Picture Vocabulary Test, and full cognitive battery (see below) will be obtained.

Visit 2 Randomization- Drug Period 1 (Study week 0)

At this visit all subjects who had successfully completed all screening tests and had no significant abnormalities on baseline laboratory, physical exam, neurologic exam, or IQ testing will be randomized to study drug. At this visit, neuropsychological testing will be conducted before the first dose of study drug is administered. Subject will be randomized, and study drug will be dispensed.

Study weeks 2 - 6

During this period, subjects will titrate up during the 1st two weeks, and be maintained on 800mg/day of ESL or Carbamazepine during weeks 3-6. The subject's doses will be titrated according to the schedule outlined below. Telephone contacts will be made at weeks 2 and 4 to check on adverse events and to encourage compliance.

Visit 3 (Study week 6)

At this visit, pill bottles will be checked, and pill counts conducted. Vital signs and a brief physical examination will be obtained. In addition, antiepileptic drug blood levels, CBC and chemistries will be obtained, and cognitive function and behavioral testing will be performed. (Cognitive function and behavioral testing will be rescheduled if the subjects inadvertently used alcohol, non-approved drugs 72 hours before testing.)

Study weeks 6 - 10

The subject will be tapered off drug over the first 3 days and then remain off drug for the next 25 days.

Visit 4 (Study week 10)

This visit ends the washout period and begins the baseline for Drug Period 2. At this visit, vital signs and a brief physical examination will be obtained. Subjects will undergo cognitive and behavioral testing and then the alternate drug treatment will be dispensed. Titration will be similar to the first titrations beginning at Visit 2. In addition, a pregnancy test will be obtained in women of child bearing potential.

Study weeks 10 - 14

During this period subjects will titrate up during weeks 10-12, and be maintained on 800mg/day of ESL or Carbamazepine during weeks 12-16. Telephone contacts will be made at weeks 12 and 14 to check on adverse events and to encourage compliance.

Visits 5 (Study week 16)

At this visit, pill bottles will be checked, and pill counts conducted. Vital signs and a brief physical examination will be obtained. In addition, antiepileptic drug blood levels, CBC and chemistries will be obtained, and cognitive function and behavioral testing will be performed. (Cognitive function and behavioral testing will be rescheduled if the subjects inadvertently used alcohol, non-approved drugs 72 hours before testing.)

Study weeks 16 - 20

The subject will be tapered off drug over the first 3 days and then remain off drug for the next 25 days.

Visit 6 (Study week 20)

This visit ends the washout period and begins the baseline for Drug Period 2. At this visit, vital signs and a brief physical examination will be obtained. Subjects will undergo cognitive and behavioral testing and then the alternate drug treatment will be dispensed. Titration will be similar to the first titrations beginning at Visit 2. In addition, a pregnancy test will be obtained in women of child bearing potential.

VII. NEUROPSYCHOLOGICAL TESTS

A. Outline:
Note that test will performed in the following order.

Computerized Testing Battery (CNS Vitals system)
- Verbal memory immediate assessment
- Visual memory immediate assessment
- Symbol digit coding assessment

 Shifting attention test
 Dual task test
 One- and two-back continuous performance test
 Verbal memory delay assessment
 Visual memory delay assessment

Non-computerized cognitive/behavioral testing
 MCG paragraph memory-immediate recall assessment
 Symbol digit modalities test
 Stroop test
 Profile of mood states (POMS) assessment
 Columbia-Suicide Severity Rating Scale
 MCG paragraph memory-delay recall assessment

B. Description of Individual Tests:

1. Components for computerized cognitive assessments:
The computerized cognitive assessments have been used in prior studies (see reference section for CNS Vitals). It consists of verbal memory immediate assessments, visual memory immediate assessments, symbol digit coding, shifting attention tasks, dual task tests, one- and two-back continuous performance tests, verbal memory delayed, and visual memory delayed. Detailed descriptions of each are below.

1a. The order of computerized testing should be as follows:
 Verbal memory immediate
    Encoding-30 seconds
    Immediate recognition-1 minute
 Visual memory immediate
    Encoding-30 seconds
    Immediate recognition-1 minute
 Symbol digit coding 2 minutes
 Shifting attention test 2 minutes
 Dual task test 2 minutes
 One- and two-back continuous performance test 5 minutes
 Verbal memory delayed 1 minute
 Visual memory delayed 1 minute

These are actual test run times and do not include reading instructions or practice tests.

1b. Verbal memory immediate assessment:
Fifteen words are presented sequentially for 2 seconds each on the computer screen and subjects are instructed to remember the words. Following their presentation, the 15 target words are presented, and the subject indicates if the word is new (not presented) or old (a member of the original presentation list). The duration of instructions and testing is approximately 3 minutes.
Results are reported as follows:

 Correct hits (immediate)
 Correct passes (immediate)
 Total Correct hits + passes (immediate) – This is a primary measure for Z score.

1c. Visual memory immediate assessment:
Fifteen shapes are presented sequentially for 2 seconds each on the computer screen, and subjects are instructed to remember the shapes. Following their presentation, the 15 target shapes are presented, and the subject indicates if the shape is new (not presented) or old (a member of the original presentation list). The duration of instructions and testing is approximately 3 minutes.
Results are reported as follows:
 Correct hits (immediate)
 Correct passes (immediate)
 Total Correct hits + passes (immediate) – This is a primary measure for Z score.

1d. Symbol digit coding:
As a measure of processing efficiency, symbols are presented on the computer screen and the subject types in numbers that correspond to each symbol based upon a response key. The duration of instructions and testing is approximately 4 minutes.
Results are reported as follows:
 Correct responses – This is a primary measure for Z score.
 Errors
 Correct responses – Errors – This is a primary measure for Z score.

1e. Shifting attention test:
As a measure of set shifting attention and executive function, the subject assesses a series of targets and rules and responds by pressing the appropriate shift key. The duration of instructions and testing is approximately 3 minutes.
Results are reported as follows:
 Correct responses
 Errors
 Correct responses – Errors – This is a primary measure for Z score.

1f. Dual task test:
This is a test that measures multi-tasking. The subject traces the track of a target with a computer mouse while simultaneously monitoring and responding each time a number from a series of sequentially presented random numbers (ie, 1 to 99) is presented which corresponds to specific criteria (ie, between 45 and 55). The duration of instructions and testing is approximately 3 minutes. During the test portion, the level of difficulty increases by increasing the speed of the target movement. There are 8 levels of difficulty.
Results are reported for each of 8 levels (X 15 second each) of increasing difficulty as follows:
 Percent of time cursor in box
 Correct responses
 Correct average reaction time
 Commission errors

 Omission errors

Summary across the 8 levels of difficulty includes:
 Total percent of time cursor in box
 Average percent of cursor in box
 Total correct responses
 Average correct reaction time
 Total commission errors
 The primary measure for this test is a Z score averaging Z scores for (% time in box) + (Correct RT) + (# Correct – Errors).

1g. One- and two-back continuous performance test:
As a measure of working memory and sustained attention, subjects are presented a series of shapes of different colors in a sequence on the computer screen. Subjects are required to press the spacebar upon seeing the target (eg, blue square), but only when a matching stimulus (eg, blue square) appears 1 position before (ie, one-back) or 2 positions before (ie, two-back). The duration of instructions and testing is approximately 6 minutes. As an example, correct responses (yes/no) are given for the following sequence of stimuli:
 Blue square=no
 Red triangle=no
 Blue square=yes
 Blue triangle=no

Results are reported as follows:
 Correct responses
 Average correct response time
 Incorrect responses
 Average incorrect response time
 Omission errors
 The primary measure for this test is a Z score averaging Z scores for (Correct RT) + (# Correct – Errors).

1h. Verbal memory delayed assessment:
As a measure of delayed memory, subjects are presented with 15 target words from the original list used to assess immediate verbal memory interspersed with 15 foils. The subject indicates if the word is new (not previously presented) or old (a member of the original presentation list). The duration of testing is approximately 1 minute.
Results are reported as follows:
 Correct hits (delayed)
 Correct passes (delayed)
 Total Correct responses– This is a primary measure for Z score.

1i. Visual memory delayed assessment:
This is a measure of delayed memory in which the 15 target shapes from the original list are presented interspersed with 15 foils. The subject indicates if the shape is new (not previously presented) or old (a member of the original presentation list). The duration of instructions and

testing is approximately 1 minute.
Results are reported as follows:
 Correct hits (delayed)
 Correct passes (delayed)
 Total Correct responses– This is a primary measure for Z score.

2. Components for non-computerized cognitive and behavioral assessments:
The non-computerized cognitive and behavioral battery performance measures consist of MCG paragraph memory, symbol digit modalities test, Stroop test, and POMS. A detailed description of each of these follows.

2a. Peabody picture vocabulary test:
At Screening, the PPVT (third edition) will be used to assess IQ at enrollment. The PPVT is an individually-administered test of receptive vocabulary (of standard English) for children and adults from 2.5 through 90 years old. This test requires examinees to examine 4 black and white pictures and choose which best represents the meaning of a stimulus word that is presented orally by the examiner (Dunn and Dunn, 1997).
This is screening measure and is not used in analyses.

2b. MCG paragraph memory:
A MCG paragraph memory test includes a matched set of short stories that were previously developed and have been shown to be sensitive to the side effects of anticonvulsants (Meador et al, 1993). On each test day, the subjects will be read 1 of the short stories. Free immediate and delayed (15-minute) recall will be obtained.
The primary measure for Z score is the % correct for delayed recall.

2c. Symbol digit modalities test:
The SDMT is a measure of cognitive processing involving coding which is sensitive to drug effects. This is a complex graphomotor transcription task that requires the subject to transcribe symbols to numbers as quickly as possible employing a combination of direct visual identification and/or short-term memorization. Symbols with empty squares are presented, and the subject's task is to fill in the corresponding number as quickly as possible during a 90-second interval (Smith, 1973). Results are scored based on number correct in 90 seconds, which is the primary measure for Z score.

2d. Stroop test:
The Stroop test is a measure of concentration effectiveness and response inhibition. The test consists of 3 pages containing 100 items. One page contains the words "RED," "GREEN," and "BLUE" arranged randomly and printed in black ink. No word follows itself within a column. The second page contains "XXXX"s written in red, green and blue ink. The final page consists of word names printed in non-congruent colors. The subject's task for the first card is to read correctly as many of the word names as possible during a 45-second interval. The second task is to read the colors of the printed "X"s as quickly as possible during an additional 45-second interval. The final task measures an interference effect by requiring the subject to inhibit the natural tendency to read the word, and to instead name the color of ink, which is incongruent with the word name. This test results in 3 scores: word, color, and word/color

contrast conditions (Golden, 1978).
The primary measure for Z score is the total # correct across all 3 conditions.

2e. Profile of Mood States:
The POMS is a checklist of 65 adjectives describing mood states (Lorr et al, 1971. The subject rates the presence of each mood state in the past week on a 5-point scale from “not at all” to “extremely.” The POMS is scored for 6 scales (fatigue, vigor, depression-dejection, anger-hostility, tension-anxiety, and confusion-bewilderment). All scales but the vigor scale are scored such that higher scores reflect greater mood disturbance; for the vigor scale, higher scores reflect less mood disturbance. The test is scored for each scale as well as for a total mood disturbance score derived from summing all scales (with reversal of the negatively scored items on the vigor scale). The POMS has been shown to be sensitive to AEDs in prior studies (Meador et al, 2014a, 2014b).
The Total score for POMS is the primary measure for Z score for this measure.

2f. Columbia-Suicide Severity Rating Scale (C-SSRS)
Suicidality will be assessed by trained study personnel using the C-SSRS (Columbia University Medical Center, 2008). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study.
This is a safety measure and is not used in the primary analysis.

VIII. STUDY MEDICATIONS

A. Description

ESL 400mg, Carbamazepine (immediate release) 200mg, and placebos will be provided by Sunovion or their designee. All AED doses and placebos will be overencapsulated in matched opaque capsules.

B. Packaging and Labeling

Medications will be provided by Sunovion in capsule bulk containers. Each will be labeled with the appropriate contents, ESL 400mg capsules, Carbamazepine 200mg (immediate release) capsules and matching placebo. All drugs will be identical capsules. Sunovion will supply plastic containers with tid daily dose sections for each patient. The clinical research pharmacy will be responsible for dispensing and labeling study drug for the study subjects.

C. Shipment and storage

Sunovion or their designee will ship all drug supplies to the site. A shipping invoice will be contained with each shipment and should be kept and matched against received drug. All investigational drug will be stored and locked in the Clinical Research Pharmacy. All unused drug supplies remaining at end of study will be destroyed by the site pharmacy personnel and written notification of the destruction will be sent to Sunovion. Study drug should be stored in

the drums it is shipped in, in a cool dry area until drug is dispensed to the study subjects.

D. Maintenance of medication dispensing records

Each clinical pharmacy site will provide medication dispensing instructions and forms for recording dispensing of study medications to the pharmacy study personnel. These records should be kept current during the study and be available for inspection. When medication is dispensed, the number of capsules of active and placebo are to be listed on the appropriate dispensing log. Returned capsules at each visit will also be recorded.

E. Return of unused medication

At each visit, subjects must return the medication packets and all unused study medication to the investigator. The accountability for returning of medication is the responsibility of the investigator. Unused study drug returned by subjects will be destroyed in accordance with remainder study drug.

F. Concomitant medication and therapy

Subjects will be instructed to limit alcohol consumption to no more than ½ ounce of absolute alcohol equivalents per day (approximately one 12 oz. beer, or 1 mixed drink) and no more than 3 ounces per week. Subjects will be instructed not to consume alcohol, caffeine, or take any over-the-counter medications for at least 72 hours prior to cognitive and behavioral testing. All concomitant medications will be recorded on the case report forms. Any concomitant medications and other agents, which are known to affect Carbamazepine or Eslicarbazepine or have significant effects on cognition may not be taken during this trial. A partial list of examples include: anticholinergics, anticoagulants, antidepressants, antiepileptics, antipsychotics, anxiolytics, central nervous system depressants, corticosteroids, doxycycline, erythromycin, H2 antagonists, lithium, methylphenidate, narcotics, quinidine, reserpine, theophylline, centrally active antihistamines, and grapefruit juice. Informed consent will emphasize that subjects should not consume grapefruit or its juice during the study.

IX. CLINICAL AND LABORATORY MEASUREMENTS

A. Clinical Measurements (Study weeks -1, 0, 6, 10, 16, 20)

Neuropsychological testing will be completed at baseline (visits 1 & 2), at the completion of each AED treatment period (weeks 6 & 16) and at the completion of each washout period (weeks 10 & 20). The neuropsychological test results from the first baseline testing (i.e., visit 1 at -2 weeks) will not be included in the analyses. All subjects will have at least 7 hours of sleep on the evening before the day of cognitive testing. (Note. If the subject does not get the required hours of sleep or takes non-approved medication, caffeine, etc., cognitive and behavioral testing will be rescheduled).

For detailed information regarding all of the cognitive tests refer to Section VII.

B. Clinical Safety Measurements

1. Physical Examinations (Study weeks -1, 0, 6, 10, 16, & 20)

A complete physical and neurological examination will be performed during pre-study screening (visit 1; week -1) and at the completion of the study (visit 6; week 20) or study discontinuation. Brief physical examinations will be performed on visits 2, 3, 4, & 5 (weeks 0, 6, 10, & 16).

A complete physical examination will consist of determinations of sitting blood pressure, weight, heart rate, assessment of physical condition (general appearance, skin and skin structure, HEENT, abdomen, cardiovascular, respiratory, musculoskeletal, genitourinary and central nervous systems). Brief physical examinations will consist of determinations of sitting blood pressure, weight, heart rate, and an assessment of physical condition, as required to determine change from the previous visit, and an assessment of adverse effects focused on skin and neurological systems.

2. Laboratory assessments (Weeks -1, 6, 10, 14, 18)

A. Blood and Urine Samples

Blood work assessments will be obtained at visits 1, 6, 16, & 20.

The hematology parameters to be determined are: RBC count, hemoglobin, hematocrit, WBC count, platelet count, cell morphology and complete WBC differential count (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils).

The chemistry parameters to be determined are: SGOT, SGPT, alkaline phosphatase, albumin, total protein, total bilirubin, sodium, potassium, chloride, calcium, phosphorous, creatinine, blood urea nitrogen, uric acid and glucose. The total chem panel will be obtained at visits 1 & 6; just SGOT & SGPT will be obtained at visits 3 & 5.

Urine Pregnancy tests will be performed on women of childbearing potential at Weeks -1, 10 & 20 (visits 1, 4 & 6).

In subjects of Asian descent, blood will be obtained to test for the HLA B*1502 allele. If present, subjects will not receive drug or continue in the study. Subjects lost for this reason will be replaced by new enrollees.

Anticonvulsant blood levels will be collected at Weeks 6 and 16 (i.e., visits 3 & 5). Carbamazepine levels are to be sent to the hospital laboratory for immediate

analysis. The Eslicarbazepine and Carbamazepine levels will be sent to an outside contract lab. Results are to be reviewed and stored by the non-blinded investigator.

C. Adverse Event Procedures

An ADVERSE EVENT (AE) is a noxious and unintended event observed in, or reported by, a subject who is participating in (or has participated in) a clinical study and/or has received study medication. The AE may be related temporarily either to immediate or long-term use of the drug; the AE may not necessarily be caused by the drug. Overdose is regarded as an adverse event. Any event meeting these criteria is to be considered an adverse event, regardless of whether or not it is considered drug related.

All adverse events should be reported on the appropriate Case Report Form; details should include the type of event, date of onset, duration, intensity, causality relationship to the study drug(s), and outcome. Wherever possible, a diagnosis rather than symptom(s) should be reported.

"Serious" means an adverse experience that is fatal or life-threatening, is permanently disabling, requires or prolongs inpatient hospitalization, or is a congenital anomaly, cancer or overdose.

If any medically serious adverse event occurs (SAE), the study medication may be discontinued and the patient treated at the discretion of the physician investigator.

ANY MEDICALLY SERIOUS ADVERSE EVENT REQUIRES IMMEDIATE NOTIFICATION OF THE FDA BY THE INVESTIGATOR.

Any serious adverse event that occurs up to two weeks following study participation must also be reported.

Specific procedures for Double-Blind Studies

Site personnel not involved in direct care of study subjects will generate a randomization code. In an acute medical emergency, the randomization code may be broken if this is considered essential for subject management. For this purpose the sealed randomization code will be provided to the investigator by the site pharmacy. If the code is broken, a record of the date, time and reason must be put into writing and sent to Sunovion. This letter will become part of the permanent study record.

All adverse events should be recorded on the appropriate Case Report Forms (CRF's) including date of onset and cessation, intensity and relationship to study drug. The action taken and clinical outcome of the adverse event will also be recorded.

The investigator will report all serious AE's to the FDA and to Sunovion without delay.

D. Medication Compliance Assessment

Compliance is to be judged by questioning the patient at the clinic visit and by the non-blinded observer's inspection of medication returned and recording missed doses on the appropriate CRF. Repeated noncompliance, or the missing of all scheduled doses of medication for three (3) consecutive days (72-hour period) would be cause for removing the subject from the study. Subjects should take all doses for 3 days before visits when cognitive function testing occurs.

E. Subject Discontinuation Criteria

1. Although they may withdraw without prejudice at any time, every effort should be made to have subjects complete the study within the bounds of safety and provisions of informed consent.

2. The investigator may discontinue the participation of any subject in this study if:

a. Any clinically significant adverse experiences are observed.

b. The subject is grossly noncompliant.

c. The subject's health would be jeopardized by continued participation.

d. Consent is withdrawn. Otherwise, subjects will be encouraged to complete the study, although they may withdraw at any time without prejudice.

3. If subject cannot tolerate the 800 mg/day dose of ESL or Carbamazepine, the dose may be reduced to 400 mg/day if the subject and physician deem appropriate. An attempt to increase the dose a week later can be made. If they choose not to reduce the dose or if the subject cannot tolerate at least 400 mg/day, then the subject will be discontinued.

4. Subject replacement.

   Subjects who are dropped from the study prior to completion of all cognitive testing will not be replaced.

5. Follow-up of discontinued patients

   Subjects who receive study drug and are discontinued from the study will have all safety assessments completed, including a complete physical examination and laboratory evaluation including chemistry, hematology with differential, urinalysis and urine pregnancy test as required at study termination. This testing should be done as soon as possible. Medical follow-up of any severe adverse events or clinically significant abnormal laboratory values will continue until the abnormality resolves, and adequate medical explanation is apparent.

Such data will be provided to Sunovion.

X. STATISTICAL EVALUATION

A. Sample Size

Estimations based on an overall composite score (sustained attention and memory [SAM] + neuropsychological) for carbamazepine-levetiracetam (Meador et al, 2007) would predict that with a sample size of 30 subjects in a 2-period crossover study, the probability is 90% that the study will detect a treatment difference at a 2-sided 0.01 significance level, if the true difference between the treatments is 0.370 units. This is based on the assumption that the SD of the difference in the response variables is 0.490. Given an estimated dropout of 30% to 40%, the planned sample size needed to enroll is 40 to 45 subjects.

The SDMT is a neuropsychological measure that has been sensitive to AED effects in multiple studies. Based on the SDMT for carbamazepine vs. nondrug in the carbamazepine-levetiracetam study, a total of 31 subjects will need to complete the 2-period crossover study. The probability is 90% that the study will detect a treatment difference at a 2-sided 0.01 significance level, if the true difference between the treatments is 3.800 units. This is based on the assumption that the standard deviation of the difference in the response variables is 5.100. Given an estimated dropout of 30% to 40%, the study would need to enroll between 42 and 47 subjects.

Based on the above 2 scenarios, the planned sample size to enroll in this study is 46 subjects to complete 30.

B. Methodology for statistical analysis

The parameters of interest are listed in Section VII. Descriptive statistics will be used to provide an overview of the primary, secondary, and other variable results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Unless otherwise specified, baseline neuropsychological data will be based on the Visit 2 assessments.

The primary outcome (pharmacodynamic) variable will be analyzed as the within subject difference between drugs in the overall neuropsychological composite Z-score for CBZ vs. ESL comparing between end of Maintenance Period scores for each drug (ie,Treatment Period 1 to Treatment Period 2). The overall composite Z-score will be computed for each condition from the individual cognitive test scores from the computerized tests and non-computerized neuropsychological tests (including the behavioral questionnaires) after transformation to Z-scores. The Z-score will be calculated using the values (mean and SD) from the average of the scores from the 3 nondrug conditions (Baseline, first Washout Period, and second Washout Period).

The primary analysis will compare the composite Z scores for ESL to Carbamazepine

for each subject at the end of the Treatment Maintenance Periods. Since the analysis is based on an overall composite score, no correction for multiple comparisons is necessary. The use of composite Z-scores avoids Type II error.

Secondary analyses will be conducted to compare the two AEDs states to the non-drug average from Visits 2, 4 & 6. The initial cognitive assessment (i.e., Visit #1) is given to reduce practice effects and will not be used in the statistical analyses. Secondary analyses will also be conducted comparing the 2 drug states to each other and the non-drug state for the individual neuropsychological variables.

Summary statistics will be calculated by treatment for each evaluation of antiepileptic blood levels (ABLs). Additional analyses of data will be performed which take the ABLs into account. Linear correlations of plasma concentrations and the overall composite and individual score variables will be plotted with a fitted regression line superimposed for each drug condition.

The incidences of all adverse events reported during the trial will be tabulated by treatment and study period. The other safety variables, which include changes in hematology, clinical chemistry, and urinalysis parameters, and vital signs will be analyzed descriptively. The actual measurement and its change from Baseline will be presented by visit and period of collection. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-Baseline status when compared with their Baseline status.

C. Interim Analysis

No interim analyses are planned.

D. Definition of Evaluable Subjects

Any subject who ingested one or more doses of blinded study medication and provided follow-up information will be evaluable for the analysis of the safety data. The primary analysis will include subjects who complete all visits for the primary variable in both periods and who did not have any important deviations, which may have an impact on cognitive function. Subjects who prematurely discontinue the study will be evaluated based on the data collected at each visit attended. Any subject who is evaluable for the safety analysis who also has baseline and end of drug period cognitive/behavioral data available for each of the two drug periods will be evaluable for the intent-to-treat analysis of the parameters of interest. Any subject evaluable for the intent-to-treat analysis will be evaluable for the per-protocol analysis of the parameters of interest provided that the subject was compliant with the protocol with regard to the study medication regimen, use of concomitant medications, sleep requirements prior to cognitive testing, alcohol consumption, caffeine consumption, and use of OTC medications prior to cognitive testing. All data will be used to their maximum possible extent, but without any imputations for missing data for any parameter.

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APPENDIX A - STUDY TIMETABLE

PROCEDURE	SCREENING		FIRST DRUG PERIOD		TAPER/ WASHOUT	SECOND DRUG PERIOD		TAPER/ WASHOUT	FINAL VISIT
Week	-1	0	1 to 6*		7 to 10	11 to 16*		17 to 20	20
Visit	1	2	3		4	5			6
Informed consents	X								
Complete Physical & Neurol. Exam	X								X [a]
Brief Physical Exam			X		X	X			
CBC, Chem	X		X [b]			X [b]			X [a]
Pregnancy Test	X [c]				X [c]				X [a c]
HLA B*1250	X[d]								
ABLs			X			X			
Cognitive & Behavioral Testing	X [e]	X	X		X	X			X
Phone call			X[f]	X[f]		X[f]	X[f]		
Study Drug Dispensed		X			X				

* Calls are made at weeks 2, 4, 12 and 14 to check on AEs and to encourage compliance.
[a] Done if patient discontinues early, or at last study visit
[b] Just CBC, SGOT & SGPT on these dates.
[c] Done only in women of child bearing potential
[d] HLA B*1250 testing in subjects of Asian descent
[e] Screening tests include Peabody IQ at first visit only, then remainder of neuropsychological battery (which is repeated each testing session)
[f] Research coordinator will call subjects on weeks 2, 4, 12 & 14 to check on side effects.