Perampanel Titration and Cognitive Effects

Protocol Version 1.8 – 02 May 2022

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PROTOCOL FOR CLINICAL RESEARCH TRIAL

Protocol Version 1.8 – 02 May 2022

TITLE: Effects of Titration Rate on Cognitive and Behavioral Side Effects of Perampanel

BRIEF DESCRIPTION OF STUDY

This is a randomized, double-blind, parallel group design across different titration rates of perampanel in healthy volunteers. The study consists of 8 visits, 4 of which will occur at the participant's home, over a 7-week period. One hundred and three (103) normal healthy subjects will be treated with perampanel (PER) at one of four different titration rates: (1) 2mg/day PER for one week followed by 4mg/day PER for five weeks, (2) 2mg/day PER for two weeks followed by 4mg/day PER for four weeks, (3) 4mg/day PER for six weeks, or (4) placebo (0mg/day PER) for six weeks. Cognitive and behavioral function testing along with safety testing will be conducted at screening, pretreatment baseline, the end of each week during the titration and maintenance period.

TIME PERIOD AND NUMBER OF SUBJECTS

A. Anticipated Number of Subjects: 103 (to obtain 76 evaluable subjects)
B. Anticipated Duration of Study: 1 Year

DESCRIPTION OF MEDICATIONS

Generic	Strength and Dosage Form	Therapeutic Classification
PER	2 mg/capsule	Anticonvulsant

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I. BACKGROUND AND RATIONALE

The efficacy of antiseizure medications (ASMs) 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 ASMs are of particular interest. The older ASMs are known to produce untoward cognitive effects, which are clinically significant in some patients (Meador, 2001). The cognitive effects of carbamazepine, phenytoin, and valproate are similar while the effects of phenobarbital are worse. Several of the newer ASMs are well tolerated and demonstrate fewer adverse cognitive effects compared to placebo and to older ASMs, but other new ASMs have significant cognitive side effects (Meador, 2020).

Perampanel (PER) is a new generation ASM, which acts as an antagonist of α-amino- 3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Phase II studies in patients with focal seizures demonstrated doses from 4-12mg/day are generally well-tolerated, with the most common adverse events being CNS-related (Krauss et al., 2012a). Additionally, in phase III studies showed that the minimum effective dose for seizure reduction is 4mg/day and that 4-12mg/day have acceptable tolerability, with adverse events of dizziness, somnolence, and fatigue showing dose-dependent effects (French et al., 2013; Krauss et al., 2012b).

Studies examining the cognitive effects of perampanel suggest that measures of cognition are minimally affected by perampanel at maintenance therapeutic doses. A retrospective comparison of the cognitive effects lacosamide and perampanel suggests that neither have negative effects on cognition (Meschede et al., 2018). However, this study was confounded by several factors, such as the use of perampanel and lacosamide as adjunctive treatments. A prospective, long-term study of the cognitive effects of perampanel in adolescents did not show an impact on a global measure of cognition, measured by a change from baseline assessments (Piña-Garza et al., 2018). Similar findings were shown in adolescents in another randomized, controlled trial in which a global cognitive measure after adjunctive treatment with perampanel was not different from placebo (Meador et al., 2016).

Cognitive side effects of drugs are affected by ASM dose and titration, However, the effects of titration and habituation on the cognitive and behavioral side effects of drugs are not well established for most ASMs, especially in regards to the timing of such effects, with the possible exception of topiramate. The present label representation of all drug-related treatment emergent adverse effects (TEAEs) across the titration and maintenance phases of clinical trials overexpresses the ultimate expected TEAEs once titration is completed and time for habituation has occurred. A more realistic and pragmatic view of TEAEs would be to denote TEAEs leading to ASM discontinuation and then separate TEAEs occurring during titration and the remaining TEAEs at maintenance once titration and time for habituation have occurred.

The present investigation is a post-marketing study in healthy volunteers designed to provide more safety information on effects of perampanel dose and titration on cognitive and other side effects, employing a randomized double-blind parallel group design at different

titration rates. 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 effects of epilepsy, underlying brain dysfunction, and changes in seizure frequency on cognitive function. In addition, examining ASM cognitive effects in healthy subjects allows extrapolation of the results to other patient populations that might be potentially treated with ASMs (e.g., tremor, pain). We have conducted multiple studies with similar design with an excellent safety record that have provided clear delineation of the cognitive side effects of ASMs (Meador, et al. 2019).

II. STUDY QUESTIONS

1. What are the behavioral, cognitive or other side effects of perampanel at different titration rates in healthy volunteers?
2. What is the time course of habituation to objective vs. subjective neuropsychological (e.g., cognitive and behavioral) side effects of perampanel?

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 across different titration rates of perampanel.

IV. STUDY DESIGN

The study will employ a randomized, double-blind, parallel group design across different titration rates of perampanel in healthy volunteers. Every subject will be treated with perampanel (PER) at one of four different titration rates: (1) 2mg/day PER for one week followed by 4mg/day PER for five weeks, (2) 2mg/day PER for two weeks followed by 4mg/day PER for four weeks, (3) 4mg/day PER for six weeks, or (4) placebo (0mg/day PER) for six weeks. A study physician will monitor each subject during ASM treatment period. Subjects will undergo cognitive, behavioral, and safety testing at screening, prior to initiation of the first dose, and at the end of each week during the titration and maintenance period. Subjects and study personnel in direct contact with subjects will be blinded to ASM 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. One hundred and three subjects across three academic medical centers (Stanford University, New York University, and Northwestern University) will be enrolled in the study in order to complete 76 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 or positive urine drug test at screening.

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

4. Prior adverse reaction to or prior hypersensitivity to perampanel.

5. Prior participation in studies involving perampanel.

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

7. Subjects with IQ $\leq$ 80 as determined by the Peabody Picture Vocabulary Test after enrollment.

8. Positive pregnancy test. Women of childbearing potential will be required to use approved birth control methods during the study.

9. Presence of lifetime history of suicide attempt (including an active attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ('Yes') to either Question 4 or Question 5 of the C-SSRS at Screening.

10. Invalid results on computerized cognitive tests at screening as indicated by a 'No' on any of the validity indicators generated in the CNS Vital Signs report and low effort on neuropsychological assessments per investigator judgement.

VI. STUDY PROCEDURES

A. Overview: time and events

The study will employ a randomized, double-blind, parallel group design across different titration rates of perampanel in healthy volunteers. The study consists of 8 visits over an 8-week time period. Subjects will be screened and tested at baseline, and then randomly assigned to receive one of four titration schedules, each lasting 6 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

Subjects will be titrated up to 4mg/day PER or receive placebo according to the dosage schedule below:

Event	1	2	3	4	5	6	7	8
Week	Screen	BL[a]	1	2	3	4	5	6
Clinic Visit	X	X			X			X
Placebo			0mg	0mg	0mg	0mg	0mg	0mg
PER[b]-1			2mg	4mg	4mg	4mg	4mg	4mg
PER[b]-2			2mg	2mg	4mg	4mg	4mg	4mg
PER[b]-3			4mg	4mg	4mg	4mg	4mg	4mg
Partial NP[c]			X	X		X	X	
Full NP[d]	X	X			X			X
TEAEs[e]	X	X	X	X	X	X	X	X

Testing is at the end of each week.
[a]BL = baseline visit.
[b]PER = perampanel.
[c]Partial NP = partial neuropsychological battery on non-clinic visit weeks refers to online CNS-Vital Signs computerized cognitive tests and behavioral questionnaires (POMS-total, AEP, & QOLIE-89 cognitive scores, which will be mailed back).
[d]Full NP = full neuropsychological battery includes Non-computerized cognitive tests and the Partial NP (questionnaires and online CNS-Vital Signs computer tests).
[e]TEAEs = treatment emergent adverse events.

The investigative team will monitor each subject's progress and safety during ASM treatment periods. Subjects will remain in their treatment arm for a total of 6 weeks.

D. Enrollment Goals

Previous studies indicate that an enrollment of 103 subjects will be required to obtain 76 evaluable subjects. See Statistical Section for power analysis.

E. Visit-Specific Treatment and Evaluation Sequence

Subjects will be randomly assigned to one of four possible titration schedules. Each titration schedule lasts 6 weeks.

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. Dosing of the study medication should be at approximately the same time of day (e.g., before the participant goes to sleep). However, due to the long half-life of perampanel, this is not critical. 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 weeks 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, full physical examination, full neurologic examination, vital signs, laboratory screening (including urine pregnancy test for women of childbearing potential), urine drug screen, IQ screen with Peabody Picture Vocabulary Test, full cognitive battery (see below), and lifetime assessment of suicidal ideation/behavior measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) will be obtained.

Visit 2 Baseline/Randomization (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. Subjects will be randomized and study drug will be dispensed.

Visit 3 Home testing (Study week 1)

At this visit, a partial neuropsychological assessment of cognitive function and behavioral testing will be performed. The assessments at this visit consist of online CNS-Vital Signs computerized cognitive tests and behavioral questionnaires (Profiles of Mood States

(POMS), Adverse Events Profile (AEP), & cognitive/behavioral subsets of QOLIE-89). Partial neuropsychological assessment will be conducted. Telephone contact will be made to check on adverse events and to encourage compliance.

Visit 4 Home testing (Study week 2)

At this visit, a partial neuropsychological assessment of cognitive function and behavioral testing will be performed. The assessments at this visit consist of online CNS-Vital Signs computerized cognitive tests and behavioral questionnaires (Profiles of Mood States (POMS), AEP, & cognitive/behavioral subsets of QOLIE-89). Partial neuropsychological assessment will be conducted. Telephone contact will be made to check on adverse events and to encourage compliance.

Visit 5 Clinic testing (Study week 3)

At this visit, a brief physical examination, brief neurologic examination, vital signs, full neuropsychological assessment of cognitive function and behavioral testing will be performed. Full neuropsychological assessment will be conducted and perampanel blood levels will be collected. Time of last dose will be collected, suicidal ideation/behavior since last visit (C-SSRS) will be obtained, and adverse events will be assessed.

Visit 6 Home testing (Study week 4)

At this visit, a partial neuropsychological assessment of cognitive function and behavioral testing will be performed. The assessments at this visit consist of online CNS-Vital Signs computerized cognitive tests and behavioral questionnaires (Profiles of Mood States (POMS), AEP, & cognitive/behavioral subsets of QOLIE-89). Partial neuropsychological assessment will be conducted. Telephone contact will be made to check on adverse events and to encourage compliance.

Visit 7 Home testing (Study week 5)

At this visit, a partial neuropsychological assessment of cognitive function and behavioral testing will be performed. The assessments at this visit consist of online CNS-Vital Signs computerized cognitive tests and behavioral questionnaires (Profiles of Mood States (POMS), AEP, & cognitive/behavioral subsets of QOLIE-89). Partial neuropsychological assessment will be conducted. Telephone contact will be made to check on adverse events and to encourage compliance.

Visit 8 Clinic testing (Study week 6)

At this visit, a full physical examination, full neurologic examination, vital signs, laboratory screening (including urine pregnancy test for women of childbearing potential), urine drug screen, full neuropsychological assessment of cognitive function and behavioral

testing will be performed. Full neuropsychological assessment will be conducted and perampanel blood levels will be collected. Time of last dose will be collected, suicidal ideation/behavior since last visit (C-SSRS) will be obtained, and adverse events will be assessed.

F. Subject Reimbursement Rates

Subject Reimbursement Rates (total $1300):

Event	1	2	3	4	5	6	7	8
Week	Screen	BL	1	2	3	4	5	6
Clinic vs Web	Clinic	Clinic	Web	Web	Clinic	Web	Web	Clinic
Payment	$100	$100	$200	$100	$200	$100	$100	$400

Provisions for prorating payment: If perampanel levels tested at visits 5 and 8 are below detectable levels, this indicates that the participant was not complying with the protocol and they will not receive their final payment of $400 for visit 8. Please note that this only applies to participants assigned to the three perampanel groups, not the placebo group.

VII. NEUROPSYCHOLOGICAL TESTS

A. Outline:

Note that test will be performed in the following order.

Computerized Testing Battery (CNS Vital Signs 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
- AEP
- QOLIE-89 cognitive domains (attention/concentration, language, memory)
- MCG paragraph memory-delay recall assessment
- Columbia-Suicide Severity Rating Scale

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 Vital Signs). 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 in addition to new words, 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 in addition to new shapes, 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 (i.e., 1 to 99) is presented which corresponds to specific criteria (i.e., 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 (e.g., blue square), but only when a matching stimulus (e.g., blue square) appears 1 position before (i.e., one-back) or 2 positions before (i.e., two-back). The duration of instructions and testing is approximately 6 minutes. As an example of two-back, 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:

This is a measure of delayed memory in which the 15 target words from the original list are presented 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 a series of 4 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:

The 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 (approximately 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 ASMs in prior studies (Meador, 2020).

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; Posner et al., 2011). This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study.

Subjects who have active suicidal ideation (answering “Yes” to questions 4 and/or 5 on the C-SSRS) will be evaluated by the Investigator. If the Investigator determines that a subject is at risk of suicide or self-harm, appropriate measures to ensure the subject’s safety and obtain mental health evaluation must be implemented and the Investigator should evaluate if the patient should be discontinued from the study.

This is a safety measure and is not used in the primary analysis.

2g. Adverse Events Profile (AEP)

The AEP measures patients' perception of adverse effects of antiepileptic drugs (Baker et al, 1997; Perucca et al, 2012). It has 19 items assessing the frequency of the most common adverse effects of antiepileptic drugs during previous weeks, using a four-point Likert scale. Item ratings can be added to obtain a total score of 19–76, higher scores indicating a greater burden of adverse effects.

2h. QOLIE-89

The QOLIE-89 inventory was developed to assess perception of quality of life issues in patients with epilepsy (Devinsky et al., 1995). It has 89 questions covering 17 different scales: health perceptions, overall quality of life, physical function, role limitations-physical, role limitations-emotional, pain, work/driving/social function, energy/fatigue, emotional well-being, attention/concentration, health discouragement, seizure worry, memory, language, medication effects, social support, and social isolation. These scales also are aggregated into an overall score. In the present study, we will employ only questions related to the subject's perception of their attention/concentration, memory, and language (Perrine et al., 1995; Elixhauser et al., 1999). The purpose of these measures in the present study is to allow us to compare subjective perceptions of cognitive side effects to objective performances (Marino et al., 2009). Where appropriate, ratings will be made based on the previous week, rather than previous 4 weeks as originally written in the QOLIE-89.

VIII. STUDY MEDICATIONS

A. Description

PER 2mg, 4mg, and placebos will be provided by Eisai or their designee. All ASM doses and placebos will be overencapsulated in matched opaque capsules.

B. Packaging and Labeling

Medications will be provided by Eisai in capsule bulk containers. Each will be labeled with the appropriate contents, PER 2mg capsules, PER 4mg capsules, and matching placebo. All drugs will be identical capsules. The clinical research pharmacy will be responsible for dispensing and labeling study drug for the study subjects.

C. Shipment and storage

Eisai 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 Eisai. 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/or 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 bottles 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. Regular consumption of caffeine is allowed but will be limited to two cups on test days. Subjects will be instructed not to consume alcohol 12 hours prior to cognitive and behavioral testing, , 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 perampanel 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, and centrally active antihistamines.

IX. CLINICAL AND LABORATORY MEASUREMENTS

A. Clinical Efficacy Measurements (Study weeks -1, 0, 1, 2, 3, 4, 5, & 6)

Neuropsychological testing will be completed at screening (visit 1; study week -1), baseline (visits 2; study week 0), and each week of the ASM treatment period (visits 3-8; study weeks 1-6). The neuropsychological test results from the first screening testing (i.e., visit 1 at -1 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, 3, & 6)

A complete physical and neurological examination will be performed during pre-study screening (visit 1; study week -1) and at the completion of the study (visit 8; study week 6) or early study discontinuation. Brief physical and neurological examinations will be performed at visit 5 (study week 3).

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 (Study weeks -1 and 6)

A. Blood and Urine Samples

Blood work assessments will be obtained at visits 1 & 8.

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 chemistry panel will be obtained at visits 1 & 8.

Urine Pregnancy tests will be performed on women of childbearing potential at study weeks -1, and 6 (visits 1 & 8).

Blinded PER blood levels will be collected at study weeks 3 and 6 (i.e., visits 5 & 8). PER levels will be sent to an outside contract lab. PER levels may be sent to the hospital laboratory for immediate analysis if testing is available. Results are to be reviewed and stored by a 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 will 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.

At enrollment, the subjects will be informed of known perampanel-adverse side effects such as dizziness, sleepiness, tiredness, irritability, falls, nausea, problems with muscle coordination, problems walking normally, vertigo, weight gain, headache, vomiting, abdominal pain, and anxiety. The potential serious adverse side effects of perampanel will be highlighted, and subjects advised to immediately contact the investigators if any serious adverse effects occur. Subjects who have homicidal or aggressive behavior will be evaluated by the Investigator. The drug will be discontinued, and if the Investigator determines that the subject or others are at risk, appropriate measures to ensure the safety of the subject and others.

Serious adverse side effects for perampanel in the controlled Phase 3 epilepsy clinical trials included hostility- and aggression- related adverse reactions occurred in 12% and 20% of patients randomized to receive perampanel at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group (FDA label, 2016). Three patients (0.1%) out of 4,368 perampanel-treated patients exhibited homicidal ideation or threat in controlled and open-label studies, including non-epilepsy studies. These effects were dose-related (less at 4mg) and generally appeared within the first 6 weeks of treatment. A review of the phase I, II, and III studies concluded that the incidence of hostility/anger was not different from placebo in doses ≤ 8 mg (Ettinger et al, 2015).

U.S. Prescribing Information for all AEDs includes the following language: "AEDs increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication."

The investigators have conducted multiple studies with healthy volunteers on the cognitive effects of antiseizure medications with an excellent safety record (see 15 References

from Prior Healthy Volunteer ASM Studies by Meador). Almost all side effects are mild or moderate and reversable. No long-term sequelae have ever occurred.

If any medically serious adverse event occurs (SAE), the study medication may be discontinued, and the subject 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.

Serious adverse events must be reported to the lead site principal investigator, Kimford Meador, within 24 hours of the site becoming award of the SAE.

Serious adverse events must be reported to sites' institutional review boards (IRB) according to their IRB's regulations.

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 Eisai. 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 Eisai 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. Subjects will be encouraged to complete the study, although they may withdraw at any time without prejudice.

4. Subject replacement.

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

Subjects who are withdrawn prior to completion of at least one set of cognitive testing on treatment drug (i.e., prior to visit 5/study week 3) may 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 Eisai.

X. STATISTICAL EVALUATION

A. Sample Size

We assume that the 4 groups (3 PER treatments and a placebo group) are equally spaced (in terms of z-score) at the time point of maximum drug effects (end week 1 for 4mg group and end week 3 for titration to 2mg x2wks then 4mg group), with a maximum difference of 0.24 (which is the difference between the placebo group and treatment at max effect). We then assume that over the 4 visits after max drug effect the z-scores get closer together until

they are equal at the treatment week 6th. The calculation indicates that at least 18 subjects are needed in each group to have 80% power. Since there are 4 groups, the total sample at least finishing assessment at end of week 6 (event 8) would be 19 X 4 = 76. Enrollment will include 20% (n=15) more to account for dropouts prior to assessment at end of visit 2 (baseline), and ~15% (n=12) more for dropouts before end of event 8 (treatment week 6). Thus, the total enrollment sample will be 103 subjects.

In summary, the 4 total groups (3 PER treatment, 1 placebo) would need at least 19 subjects per group (76 total), and total enrollment would be rounded to 105 to account for dropouts.

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.

Study question 1: What are the behavioral, cognitive or other side effects of perampanel at different titration rates in healthy volunteers?

The primary outcome variable will be the overall neuropsychological composite z-scores for the objective and subjective measures combined.

Study question 2: What is the time course of habituation to objective vs. subjective neuropsychological (e.g., cognitive and behavioral) side effects of perampanel?

The primary outcome variable will be the neuropsychological composite z-scores for the objective and subjective measures, which will be analyzed separately.

The objective measure z-score will be calculated by averaging overall computerized and noncomputerized cognitive z scores, which are calculated by averaging individual z-scores of selected performance measures from the computerized cognitive test battery (i.e., average of z-scores for the domain scores for executive function and for processing speed) and from the noncomputerized cognitive test battery (i.e., average of individual z-scores for MCG immediate, MCG delayed, SDMT, and Stroop-average score). The subjective measure z-score will be calculated by averaging the individual z-scores for AEP, POMS, and QOLIE-cognitive questions (average of 3 scores from QOLIE). These z-scores will be assessed by a 4 (titration rate) X 6 (time: weeks 1-6) ANCOVA controlling for scores at Baseline (visit 2) using an intent-to-treat analysis for those receiving neuropsychological testing at least at the end of week one. Imputations will be employed for dropout after week one.

We will control for differences across groups in age, gender, and personal/family history of psychiatric disorders.

This method with a similar overall score has been employed in prior investigations. This approach avoids potential Type I errors from multiple statistical comparisons and Type II errors resulting from reduced statistical sensitivity as a result of correcting for multiple comparisons. Analyses of individual components of the computer and neuropsychological assessment are secondary endpoints meant to evaluate sensitivity of the primary endpoint and examine the pattern of neuropsychological effects. All other endpoints are supportive and are safety assessments. Hence no adjustments for multiplicity are planned. P-values for these safety variables are not meant to show superiority and thus testing each of these variables at the p=0.05 level without multiplicity adjustment is a more conservative approach, which is appropriate for safety assessments and for secondary analyses of the pattern of impairments. The importance of the results should be evaluated in terms of actual differences and the risk/benefits offered by the drug to the patients.

The secondary outcome variables will be:

1. Compare titration rates for changes from Baseline (visit 2) to the end of titration (study week 3) and end of maintenance (study week 6) using Z-scores from full neuropsychological battery. The outcome variable for this analysis will be an overall neuropsychological composite Z-score, calculated by averaging individual z-scores of the selected performance measures from the computerized cognitive test battery (i.e., z-scores for the domain scores for executive function and processing speed), the average for individual Z-scores for AEP, POMS, QOLIE-cognitive questions (average of 3 scores), and the noncomputerized cognitive scores (i.e., average of z-scores for MCG immediate, MCG delayed, SDMT, Stroop-average score).
2. Compare titration rates for TEAEs and dropouts due to TEAEs across visits 3-8 (i.e., weeks 1-6).
3. Separate comparisons of titration rates for behavioral overall scores and cognitive overall scores.
4. Comparisons of titration rates and habituation over time for individual measures.

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 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 or at least one set of cognitive/behavioral testing on treatment drug 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 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

Event	1	2	3	4	5	6	7	8
Week	Screen[a] -1	BL[b] 0	1	2	3	4	5	6
Day[c]	-7	0	7	14	21	28	35	42
Clinic Visit	X	X[m]			X			X
Home Testing			X	X		X	X	
Informed Consent	X							
PMHx & Fam Hx[d]	X							
Vital Signs	X				X			X
Full PE[e]	X							X
Neuro Exam[f]					X			
CBC & Chems[g]	X							X
PER Level[h]					X			X
Urine drug screen	X							X
Urine pregnancy test[i]	X							X
C-SSRS[j]	X				X			X
Partial NP[k]			X	X		X	X	
Full NP[l]	X	X			X			X
TEAEs	X	X	X	X	X	X	X	X
Dispense Drug		X						

[a]Screening visit may occur 1-3 weeks prior to baseline visit.
[b]BL = baseline visit.
[c]Visits may occur +/- 3 days from target day.
[d]PMHx & Fam Hx = psychiatric history for subject and their family
[e]PE = complete physical exam including full neurologic exam
[f]Neuro Exam = brief neurological exam including brief physical exam
[g]CBC & Chems = CBC with differential and Chemistries (comprehensive metabolic panel)
[h]PER Level = perampanel blood level
[i]Women of childbearing potential only
[j]C-SSRS = Columbia-Suicide Severity Rating Scale
[k]Partial NP = partial neuropsychological battery on non-clinic visit weeks refers to online CNS-Vital Signs computerized cognitive tests and behavioral questionnaires (POMS-total, AEP, & QOLIE-89 cognitive scores, which will be mailed back). Note phone calls will be made for each home testing visit to assure adherence to the protocol.
[l]Full NP = full neuropsychological battery includes non-computerized cognitive tests and the items from the Partial NP (questionnaires and online CNS-Vital Signs computer tests). Peabody Picture Vocabulary Test (PPVT) given only at screening visit.
[m]This week does not require clinic room or to see physician unless necessary.

APPENDIX B - PROTOCOL SIGNATURE FORM

PROTOCOL TITLE: Effects of Titration Rate on Cognitive and Behavioral Side Effects of Perampanel

VERSION: 1.8

VERSION DATE: 02 May 2022

I have read the protocol described above and agree to conduct this study in accordance with the procedures described therein. I also agree to conduct the study in compliance with all applicable regulations.

_____

Investigator's Name

_____ _____

Investigator's Signature Date