

A Phase IV Study

Feasibility Study to Evaluate the Efficacy and Safety of Perampanel in Seizure Patients with Primary Glial Brain Tumors

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2 LIST OF ABBREVIATIONS

AE	Adverse Event
AED	Anti-epileptic Drug
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BCS	Brain Subscale
BDI	Beck Depression Inventory
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CPC	Cancer Protocol Committee
CTCAE	Common Terminology Criteria for Adverse Events
DCI	Duke Cancer Institute
DOCR	Duke Office of Clinical Research
DSMB	Data and Safety Monitoring Board
DUHS	Duke University Health System
DUMC	Duke University Medical Center
FACT-Br	Functional Assessment of Cancer Therapy-Brain
FACT-Cog	Functional Assessment of Cancer Therapy-Cognition
FACIT-F	Functional Assessment of Cancer Therapy-Fatigue
FDA	Food and Drug Administration
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IRB	Institutional Review Board
KPS	Karnofsky Performance Status
NCI	National Cancer Institute
p.o.	per os/by mouth/orally
PRO	Patient-Reported Outcome
PRTBTC	Preston Robert Tisch Brain Tumor Center
QoL	Quality of Life
SAE	Serious Adverse Event
TEAE	Treatment-Emergent Adverse Events

3 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

3.1 Purpose

This is a Phase 4 single-arm study assessing the efficacy of perampanel as an adjunctive anti-epileptic drug (AED) in patients with primary glioma presenting refractory partial onset seizure activity.

Primary Objective:

1. To determine the efficacy of perampanel as an adjunctive AED in patients with primary glioma presenting refractory partial onset seizure activity.

Secondary Objective:

1. To assess the safety and tolerability of perampanel as an adjunctive AED in patients with primary glioma presenting with refractory partial onset seizure activity.

Exploratory Objective:

1. To evaluate the effect that perampanel has on neurocognition and patient-reported outcomes of quality of life (QoL) in patients with primary glioma presenting with refractory partial onset seizure activity.

Hypothesis:

We hypothesize that the addition of perampanel as an adjunctive AED will be effective in treating patients with primary glioma that are presenting with refractory partial onset seizure activity on non-enzyme inducing anti-epileptic drug regimen.

3.2 Design and Procedure

This is a Phase 4 single-arm study to assess the efficacy of perampanel as an adjunct anti-epileptic in patients with primary glioma that are presenting refractory partial onset seizure activity (defined as 3 or more seizures in a 28-day period). In this study, patients will be started on a dose of 2 mg of perampanel daily taken orally at bedtime for 2 weeks. At the start of week 3 Perampanel will be titrated up in dose in 2mg increments per week up to 8mg daily, as long as it is well tolerated by the patient. The highest dose of perampanel will be 8 mg orally at bedtime. Patients will begin the treatment period of the study starting at week 5 and will continue through the end of week 12. The planned treatment dose is 8mg, but the dose can be modified by the physician based on patient reported tolerability. Patients will be assessed in the Brain Tumor Center Clinic every 8 weeks. Study assessments will be made at enrollment, 8 weeks, 16 weeks, and 24 weeks.

Assessments will include history and physical examination (H&P) including Karnofsky Performance Status (KPS), neurological examination, evaluation of seizure history, patient-reported outcomes of QoL, and neurocognitive testing using CNS Vital Signs®. After a total of 16 weeks of therapy, perampanel will be tapered for 3 weeks and then will be discontinued, such that at week 20, patients will only be taking their original AED regimen. Patients will then be monitored through Week 24. Patients will remain on their original AED therapy during this treatment time and the dose of their original AED regimen at the start of the study will not be changed while they are on study. If seizure control is achieved during the treatment period or if seizures occur during the tapering period, patients can be continued on perampanel per the discretion of the treating physician. In this instance, perampanel will be prescribed by the treating physician and not provided within the confines of the study. Efficacy will be assessed using a log of patient-reported seizure activity. As is standard procedure at the PRTBTC, patients will be given a log to record the number of seizures that occur. Research team members will regularly contact patients for reminders and reports from the log. Safety will be assessed with the following laboratory evaluations: complete blood count (CBC) with differential, complete metabolic panel (CMP), and toxicity assessment.

3.3 Selection of Subjects

Inclusion Criteria:

1. Patients must be diagnosed with a primary glioma and have refractory partial onset seizure activity (defined as 3 or more seizures in a 28-day period) on non-enzyme inducing anti-epileptic regimen that can

include, but not limited to the following: levetiracetam (Keppra) or Keppra XR, lamotrigine (Lamictal) or Lamictal XR, gabapentin (Neurontin), tiagabine (Gabitril), topiramate (Topamax), valproic acid (Depakene) / valproate (Depacon), zonisamide (Zonegran), lacosamide (Vimpat), and clonazepam (Klonopin)

2. Adult patients (\geq 18 years old)
3. Karnofsky \geq 70%
4. Hematocrit \geq 29%, ANC \geq 1,500 cells/L, platelets \geq 100,000 cells/L
5. Serum creatinine \leq 1.5 mg/dL, serum AST and bilirubin \leq 1.5 times the upper limit of normal
6. If sexually active, patients will take contraceptive measures for the duration of protocol treatment and continue until two months after treatment. The effectiveness of hormonal contraceptives containing levonorgestrel has been shown to be reduced by perampanel at a 12 mg dose.¹ Therefore, alternative or back-up methods of contraception are recommended.
7. Signed informed consent approved by the Duke Institutional Review Board

Exclusion Criteria:

1. Pregnant or breastfeeding (Both perampanel and levetiracetam are classified as Pregnancy Category C drugs.)
2. Chronic excessive use of psycho-pharmaceuticals, alcohol, illicit drugs, or narcotics
3. Inability to complete or perform measures of patient-reported outcomes or neurocognitive testing on the computer
4. Known allergy to perampanel
5. Concomitant use of known cytochrome P450 (3A4,5,7) inducers such as carbamazepine, phenytoin, or oxcarbazepine (see Appendix A)
6. Previous history of suicidal ideation, homicidal ideation, depression leading to hospitalization or mood disturbance leading to hospitalization.

3.4 Risk/Benefit Assessment

The full prescribing information for Perampanel (FYCOMPA™) includes the following boxed warning¹:

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA
- These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression
- Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA
- Closely monitor patients particularly during the titration period and at higher doses
- FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening

The most common adverse reactions that are associated with perampanel occurring in 10% of patients or greater are dizziness (36%), somnolence (16%), and fatigue (10%). Less common reactions are irritability (9%), falls (7%), nausea (7%), ataxia (5%), balance disorder (4%), gait disturbance (4%), vertigo (4%), and weight gain (4%).

With concomitant use, perampanel, at a dose of 12 mg/day, reduced levonorgestrel exposure by approximately 40%. Use of perampanel with oral or implant contraceptives containing levonorgestrel may render them less effective. Therefore, additional non-hormonal forms of contraception are recommended (please see the FYCOMPA FDA-approved labeling dated 6/11/2013).¹

The concomitant use of known CYP enzyme inducers including carbamazepine, phenytoin, or oxcarbazepine with perampanel decreased the plasma levels of perampanel by approximately 50~67%. The starting doses for perampanel should be increased in the presence of enzyme-inducing AEDs.¹ When these enzyme-inducing

AEDs are introduced or withdrawn from a patient's treatment regimen, patient should be closely monitored for clinical response and tolerability. Dose adjustment of perampanel may be necessary. As noted, however, the decrease in the therapeutic effect seen in patients on concomitant treatment, was not affected by use of higher doses (8 mg to 12 mg).¹

Concomitant use of perampanel with other strong CYP3A inducers (e.g., rifampin, St. John's wort) should be avoided.¹

The concomitant use of perampanel and CNS depressants including alcohol may increase CNS depression.¹ A pharmacodynamic interaction study in healthy subjects found that the effects of perampanel on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol. Multiple dosing of perampanel 12 mg/day also enhanced the effects of alcohol to interfere with vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when perampanel is used in combination with other CNS depressants. Care should be taken when administering perampanel with these agents. Patients should limit activity until they have experience with concomitant use of CNS depressants (e.g. benzodiazepines, narcotics, barbiturates, sedating antihistamines). Advise patients not to drive or operate machinery until they have gained sufficient experience on perampanel to gauge whether it adversely affects these activities.¹

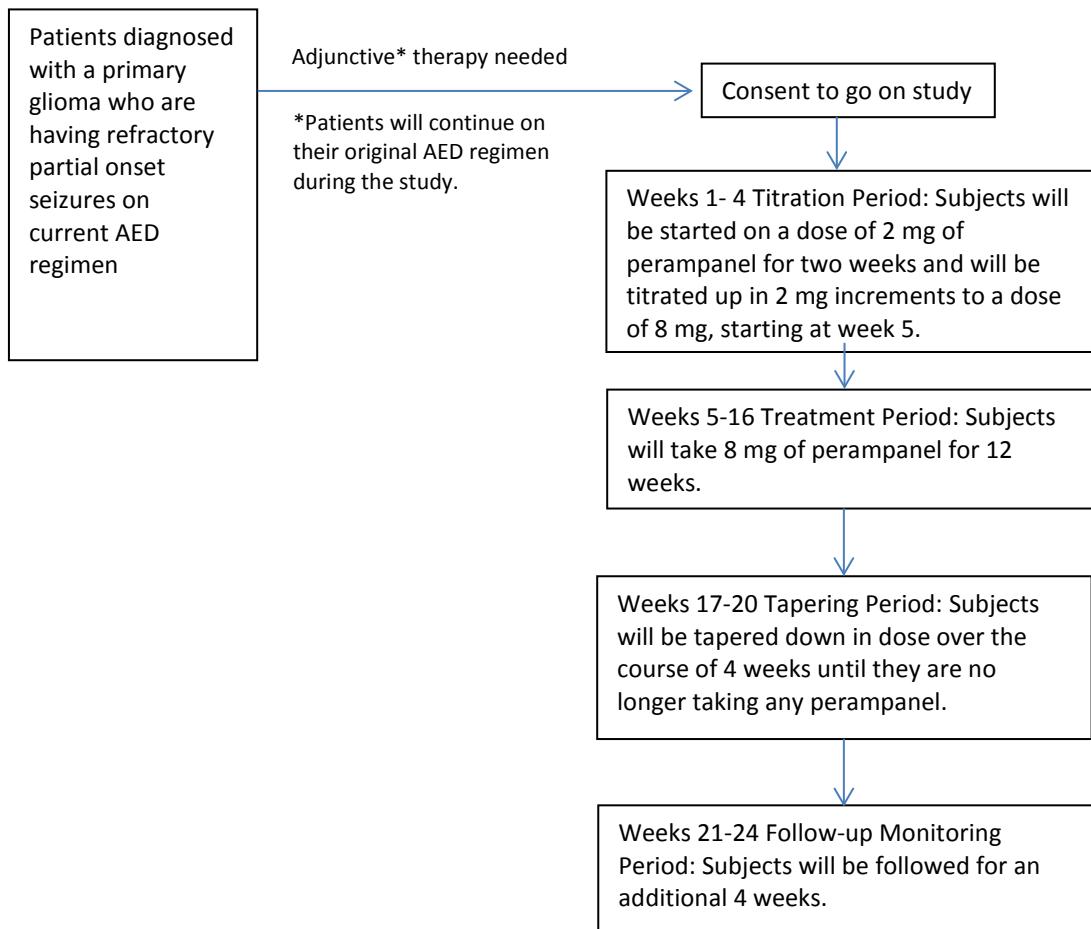
3.5 Data Analysis and Statistical Considerations

The one-arm study will assess the efficacy of perampanel for the treatment of primary brain tumor patients with partial onset seizures. The basis for this assessment is the percentage of patients with a $\geq 50\%$ seizure reduction during the treatment period compared with seizure frequency before initiation of perampanel (i.e. 50% responder rate).

Several recent conducted randomized studies of patients with partial-onset seizures have reported a 50% responder rate of approximately 20% within the standard treatment arm.²⁻⁴ Steinhoff (2009) also reports a 50% responder rate of approximately 35% within a general population of patients with partial-onset seizures treated with perampanel.⁵

This study has been designed with 90% power to detect an increase in the 50% responder rate during the treatment period from a benchmark of 20% to 35%. Assuming a type I error rate of 0.1, 61 patients will be required. Based on prior studies the early discontinuation rate was 16%, therefore 71 patients will be enrolled to compensate for patients discontinuing prior to the completion of the treatment period.

4 STUDY SCHEMA



5 BACKGROUND AND SIGNIFICANCE

5.1 Study Disease

Of the neurological symptoms seen in brain tumor patients, seizures have remained a common occurrence. In 30% of patients, seizure is the presenting symptom and another 30-50% of patients develop seizures during the disease trajectory. Furthermore, many patients with brain tumor experiencing seizures will continue to have seizures despite being on antiepileptic drug (AED).⁶ Even though there is a wide availability of anti-seizure medications, patients, in particular brain tumor patients with epilepsy, can have treatment refractory seizures. Therefore, there is a great need for newer AEDs with different novel mechanisms to treat seizures in this specific population.

5.2 Study Agent

Perampanel, a highly selective non-competitive α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) type glutamate receptor antagonist, has shown efficacy in a randomized phase III study for refractory partial-onset seizures.⁷ For most brain tumor patients suffering from seizures, the most common type is partial-onset seizures, which can be either simple or complex. The use of AMPA type glutamate receptor inhibition is particularly intriguing in that glutamate release appears to be responsible for epileptic activity in murine glioma models.⁸ Tissue isolated from tumor bearing mice exhibited increased glutamate release and presented with peritumoral hyperexcitability.⁹ Therefore, perampanel appears to be a viable candidate for seizure treatment in patients with brain tumors from both a clinical and a biological perspective.

5.2.1 Pre-clinical experience

Not applicable

5.2.2 Clinical experience

Perampanel is currently FDA-approved for the adjunctive treatment of refractory partial seizures in patient \geq 12 years of age. In a pooled analysis of three phase III studies involving 1,478 patients, median change in partial seizure frequency was greater with perampanel in comparison to placebo.² Specifically, median change in partial seizure frequencies was as follows: perampanel 4 mg, -23.3%; perampanel 8 mg, -28.8%; perampanel 12 mg, -27.2%; and placebo, -12.8%. Moreover, 50% responder rates were as follows: perampanel 4 mg, 28.5%; perampanel 8 mg, 35.3%; perampanel 12 mg, 35.0%; and placebo, 19.0%. In this pooled analysis, perampanel was well tolerated with the most frequent treatment-emergent adverse events (TEAEs) being dizziness, somnolence, and headache. Of note, there were no deaths reported and no clinically meaningful mean change in laboratory values, electrocardiography (ECG) findings, or vital signs.¹⁰ TEAEs from the pooled analysis are listed in the table below for perampanel dose 2 mg to 12 mg and placebo.

Adverse Event, n (%)	Placebo (n=442)	Perampanel 2 mg (n=180)	Perampanel 4 mg (n=172)	Perampanel 8 mg (n=431)	Perampanel 12 mg (n=255)
Any TEAE	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headache	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	34 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Fall	15 (3.4)	2 (1.1)	3 (1.7)	22 (5.1)	26 (10.2)
Nasopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)

tract infection					
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

Most TEAEs were mild to moderate and appeared to be dose related. From the pooled analyses, discontinuation of perampanel at 4 mg was 2.9%, at 8 mg was 7.7%, and at 12 mg was 19.2% in comparison to placebo.¹⁰ Common discontinuation TEAEs were dizziness, convulsion, and somnolence.

Behavioral and psychiatric TEAEs are very important to consider with AEDs as several AEDs carry boxed warning for serious or life-threatening psychiatric and behavioral adverse reactions. Perampanel carries a similar warning to other AEDs and monitoring is recommended for serious or life-threatening psychiatric and behavioral adverse reactions including but not limited to suicidal ideation and homicidal ideation.¹⁰ In the pooled analyses, there were three serious cases of aggression and one case of suicidal ideation. Perampanel is classified as a schedule III controlled substance as it causes euphoria in selected patients from phase III clinical trials.⁷

5.3 Study Purpose/Rationale

The new generation of AEDs that are devoid of P450 enzyme induction properties (levetiracetam, lacosamide, etc.) are now recommended as the AEDs of choice in primary brain tumor patients, as they do not have interactions with standard chemotherapeutic agents (irinotecan, topotecan, etc.) or cancer-specific targeted agents (dasatinib, erlotinib, etc.).¹¹ Seizure control is an important component in the quality of life for both low-grade and high-grade brain tumor patients. In fact, seizure control is the most important predictor of quality of life in recurrent low-grade glioma patients.¹² Therefore, the study of newer AEDs in the brain tumor population is greatly needed. Therefore, we seek to evaluate the efficacy of perampanel as an adjunctive AED for the treatment of refractory partial onset seizures in primary glial tumor (glioma) patients.

6 OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Analysis
Primary	To determine the efficacy of perampanel as an adjunctive AED in patients with primary glioma presenting refractory partial onset seizure activity	Percentage of patients with ≥50% seizure reduction during the treatment period compared with seizure frequency before initiation of perampanel (i.e. 50% responder rate)	See Section 13.4
Secondary	To assess the safety and tolerability of perampanel as an adjunctive AED in patients with primary glioma presenting with refractory partial onset seizure activity	The percentage of patients who experience a adverse event possibly, probably, or definitely attributable to perampanel treatment	See Section 13.5
Exploratory	To evaluate the effect that perampanel has on neurocognition and patient-reported outcomes of quality of life (QoL) in patients with primary glioma presenting with refractory partial onset seizure activity	Mean change from baseline for each neurocognitive and QoL subscale score at each follow-up assessment	See Section 13.6

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a Phase 4 single-arm study assessing the efficacy of perampanel as an adjunct anti-epileptic drug (AED) in patients with primary glioma presenting refractory partial onset seizure activity (defined as 3 or more seizures in a 28-day period). All primary glioma patients that have refractory partial onset seizures can be considered for this clinical trial if they meet the eligibility criteria. This will include patients that are receiving active chemotherapy, which could include, but is not limited to, the following agents: temozolamide, bevacizumab, irinotecan, etoposide, lomustine, carboplatin. All concomitant medications will be recorded during the study. The study will enroll approximately 71 patients at the PRTBTC at Duke.

Perampanel will be given according to FDA-approved guidelines over a 24-week period. Patients will be started on a dose of 2 mg daily taken orally at bedtime for 2 weeks. At the start of week 3 Perampanel will be titrated up in dose in 2mg increments per week up to 8mg daily, as long as it is well tolerated by the patient. Weeks 1 and 2, patients will take 2mg, Week 3 they will take 4 mg, Week 4 they will take 6mg and starting at week 5 they will take 8mg. Highest dose will be 8 mg orally at bedtime. Starting at week 5, patients will begin the treatment period, which goes from day 1 of Week 5 through day 7 of Week 16. Patients will be assessed in the Brain Tumor Center Clinic every 8 weeks. Assessments will be made at enrollment, 8 weeks, 16 weeks, and 24 weeks. Assessments will include history, physical examination, neurological examination, evaluation of seizure history, patient-reported outcomes of quality of life, and neurocognitive testing using CNS Vital Signs®. After a total of 16 weeks on therapy, perampanel will be tapered down. At Week 17, patients will begin taking 6mg of perampanel, Week 18 4mg, Week 19 2mg, and Week 20 they will no longer take perampanel. Patients will be considered off treatment at the end of week 20, once perampanel has cleared their system. The planned treatment dose is 8mg, but the dose can be modified by the physician based on patient reported tolerability. Titration and taper periods will be determined by the physician in the case where patients do not reach the planned treatment dose of 8 mg daily. Patients will continue to take their original AED regimen after they stop perampanel. Patients will then be monitored through Week 24. Patients will remain on their original AED regimen during this treatment time and the dose of their original AED at the start of the study will not be changed while they are on study. If seizure control is achieved during the treatment period or if seizures occur during the tapering period, patients can be continued on perampanel per the discretion of the treating physician. In this instance, perampanel will be prescribed by the treating physician and not provided within the confines of the study. As is standard procedure at the PRTBTC, patients will be given a log to record the number of seizures that occur. Research team members will regularly contact patients for reminders and reports from the log.

7.1.1 Missed Doses

Patients will have a dedicated clinical research nurse and coordinator who will schedule all of their appointments and a calendar will be provided to the patients. If a patient misses a dose of perampanel medication, the PI of the study will assess each situation with the research team. If the number of missed doses is less than 3, then the patient can remain on study and perampanel will continue to be given by the study protocol regimen. If the patient misses more than 3 doses of perampanel, they will no longer remain on the clinical trial. Patients will be given daily medication logs to record the date and time that they take each dose of perampanel, as well as their other AEDs.. At each study visit, they will be asked about all medications that they are taking.

7.1.2 Concomitant Medications

With concomitant use, perampanel, at a dose of 12 mg/day, reduced levonorgestrel exposure by approximately 40%. Use of perampanel with oral or implant contraceptives containing levonorgestrel may render them less effective. Therefore, additional non-hormonal forms of contraception are recommended (please see the FYCOMPA FDA-approved labeling dated 2/12/2014).¹

The concomitant use of known CYP enzyme inducers including carbamazepine, phenytoin, or oxcarbazepine with perampanel decreased the plasma levels of perampanel by approximately 50~67%. The starting doses for perampanel should be increased in the presence of enzyme-inducing AEDs.¹ When these enzyme-inducing AEDs are introduced or withdrawn from a patient's treatment regimen, patient should be closely monitored for clinical response and tolerability. As noted, however, the decrease in the therapeutic effect seen in patients on concomitant treatment, was not affected by use of higher doses (8 mg to 12 mg).¹

Concomitant use of perampanel with other strong CYP3A inducers (e.g., rifampin, St. John's wort) should be avoided.¹

The concomitant use of perampanel and CNS depressants including alcohol may increase CNS depression.¹ A pharmacodynamic interaction study in healthy subjects found that the effects of perampanel on complex tasks such as driving ability were additive or supra-additive to the impairment effects of alcohol. Multiple dosing of perampanel 12 mg/day also enhanced the effects of alcohol to interfere with vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when perampanel is used in combination with other CNS depressants. Care should be taken when administering perampanel with these agents. Patients should limit activity until they have experience with concomitant use of CNS depressants (e.g. benzodiazepines, narcotics, barbiturates, sedating antihistamines). Advise patients not to drive or operate machinery until they have gained sufficient experience on perampanel to gauge whether it adversely affects these activities.¹

Perampanel is FDA-approved as adjunctive therapy for refractory partial onset seizures, so it will be utilized in concert with other AEDs.

If subjects are receiving chemotherapy during the study, these medications, the doses, and any associated serious adverse events will be recorded.

7.1.3 Study Drug Blinding

Not applicable.

7.1.4 Randomization

Not applicable.

7.2 Rationale for Selection of Dose, Regimen, and Treatment Duration

Please see Section 5.2.2.

7.3 Rationale for Correlative Studies

In order to capture fully the many aspects of QOL, we will utilize multiple questionnaires to evaluate issues of fatigue, cognition, and mood. The Functional Assessment of Cancer Therapy-Brain (FACT-Br) has been used extensively and has been documented to identify key QOL problems for brain tumor patients.¹⁶ Other standardized questionnaires will include Functional Assessment of Cancer Therapy-Fatigue, Functional Assessment of Cancer Therapy-Cognition, and Beck Depression Inventory. Additionally, neurocognition will be measured using computer-based models known as CNS Vital Signs®. These measurements have been validated and are being used extensively in our research in not only brain tumor patients, but also in patients with other forms of cancer.¹⁷

Quality of Life will be assessed by the Functional Assessment of Cancer Therapy-Brain (FACT-BR) scale. The FACT-BR (version 4) contains subscales for physical (7-items), functional (7-items), emotional (6-items), and social/family (7-items) well-being. In addition, this instrument contains an 23-item brain cancer subscale (BCS) which assess symptoms commonly reported by brain cancer patients.¹⁶ Cancer-related fatigue will be

assessed by the 13-item Fatigue Scale using the Functional Assessment of Cancer Therapy-Fatigue (FACT-Fatigue) subscale, version 4.¹⁸ Cognitive problems will be assessed using version 3 of the Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) subscale.¹⁹ This includes subscales for perceived cognitive impairments (20 items), comments from others (4 items), perceived cognitive abilities (9 items), and impact of quality of life (4 items). Beck depression inventory (BDI) will be used to evaluate for underlying depressive symptoms. We will use the revised version (BDI-II) and the scores will range from 0 (no depression) to 63 (severe depression).²⁰ The BDI contains 21 questions in regards to mood symptoms and is multiple-choice and self-reported.

Neurocognitive testing will include the performance on the following testing using a computerized battery CNS Vital Signs®.²¹ This battery consists of seven tests that measure verbal and visual memory, finger tapping, symbol digit coding, the Stroop Test, a test of shifting attention, continuous performance test. Verbal memory test will assess verbal learning, memory for words, immediate recall, and delayed recall. Visual memory tests will assess visual learning, memory for geometric shapes, immediate recall, and delayed recall. Finger tapping test will assess motor speed and fine motor control. Symbol digit coding test will evaluate complex attention, visual-perceptual speed, and information processing speed. Stroop Test will assess executive function, simple and choice reaction time, speed-accuracy trade-off, information processing speed, and inhibition/disinhibition. Shifting attention test will assess executive function, reaction time, and information processing speed. Continuous performance test will assess sustained attention and choice reaction time. Normative data is available for this testing through CNS Vital Signs® and patients' performance will be compared to this normative data.

7.4 Definition of Evaluable Subjects, On Study, and End of Study

All patients who complete the treatment period will be included in the primary endpoint analysis. All patients who received protocol treatment, regardless of duration, will be included in the safety analysis.

7.5 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 10.7, which describes procedures and process for prematurely withdrawn patients.

8 STUDY DRUG

8.1 Names, Classification, and Mechanism of Action

Perampanel (FYCOMPA™) is a non-competitive AMPA glutamate receptor antagonist. Perampanel is described chemically as 2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl) benzonitrile hydrate.

8.2 Packaging and Labeling

The dose forms included in this study are packaged as follows:

- 2 mg Tablets: orange, round, biconvex, film-coated tablets debossed with "2" on one side and "€ 275" on the other
- 4 mg Tablets: red, round, biconvex, film-coated tablets debossed with "4" on one side and "€ 277" on the other

8.3 Supply, Receipt, and Storage

2 mg tablets are supplied as follows:

- Bottles of 30 NDC 62856-272-30
- Bottles of 90 NDC 62856-272-90

4 mg tablets are supplied as follows:

- Bottles of 30 NDC 62856-274-30
- Bottles of 90 NDC 62856-274-90

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Study supplies of perampanel will be stored by ICS.

8.4 Dispensing and Preparation

Subjects will receive perampanel as an oral therapy and will be dispensed supplies of tablets sufficient to continue therapy until their next appointment. Perampanel will be self-administered by the patient. Subjects will be given a Daily Medication Log on which they will record the amount of perampanel, as well as other AEDs that they took each day. Subjects will be asked to bring their Logs to each study visit, during which they will be reviewed by a member of the study team.

8.5 Compliance and Accountability

Drug accountability records will be maintained for all clinical trial supplies. All empty and partially used clinical trial supplies will be returned to Eisai or destroyed.

8.6 Disposal and Destruction

The ICS pharmacy will maintain detailed documentation of the number and identification of tablets and tablets that are destroyed, and copies of these documents will be provided to Eisai, upon request.

9 SUBJECT ELIGIBILITY

Please see Section 3.3 for a complete list of inclusion and exclusion criteria.

10 SCREENING AND ON-STUDY TESTS AND PROCEDURES

Table 1: Study Assessment Schema

	Baseline within 4 weeks of initiation of study drug	8 weeks after initiation of study drug	16 weeks after initiation of study drug	24 weeks after initiation of study drug
CBC with diff	X	X	X	X
CMP	X	X	X	X
H&P, including KPS and concomitant medications	X	X	X	X
Complete Neurological Examination	X	X	X	X
Toxicity assessment using CTCAE v.4 guidelines			Ongoing ²	
Urine pregnancy test ¹	X			
Seizure History/Log	X ³		Ongoing ⁴	
QoL Questionnaires	X	X	X	X
Neurocognitive Testing	X	X	X	X

¹ For women of childbearing potential, within 48 hours prior to initiation of study drug, if contraception not initiated at time of negative test result prior to that time. Urine pregnancy test will be conducted according to Duke IRB and DOCR guidelines.

² Toxicities will be recorded from the time the subject starts study drug.

³ Number of seizures in past 28 days

⁴ Subjects will be given a seizure log to record the number of seizures that occur, as is standard procedure at the PRTBTC.

10.1 Screening Examination

The screening examination will take place within 4 weeks of initiation of study drug. An informed consent must be signed by the patient before any screening procedures take place. Subject data to be collected at the Screening Examination includes the following:

Pre-treatment evaluations to determine eligibility will include the following:

- History and physical exam, including KPS and a full neurologic assessment
- Seizure history
- CBC with differential, CMP, Beta-HCG if appropriate (within 48 hours of beginning study drug, if contraception not initiated at time of negative test result prior to that time). Urine pregnancy test will be conducted according to Duke IRB and DOCR guidelines.
- Quality of life measurements and neurocognitive testing, as a baseline

If a subject is found to be ineligible to participate in the study, minimal records regarding the subject and the reason for screen failure will be retained in the study database.

10.2 Run-In Period

Not applicable.

10.3 Treatment Period

Day 1

- Subjects will be started on a dose of 2 mg of perampanel daily taken orally at bedtime for 2 weeks.
- Subjects will then be titrated up in dose in 2 mg increments each week up to 8 mg daily. Week 3 4mg daily, Week 4 6 mg daily and starting week 5 8 mg daily. The highest dose of perampanel will be 8 mg orally at bedtime.

Week 8 assessments) (+ 1 week)

- History and physical exam, including KPS and a full neurologic assessment, with collection of seizure log (subjects will keep a seizure log throughout the study)
- Toxicity assessment using CTCAE v.4 guidelines (continuous throughout study)
- CBC with diff
- CMP
- Quality of life measurements and neurocognitive testing

Week 16 assessments) (+ 1 week)

- After a total of 16 weeks on therapy, subjects will now be tapered off of perampanel over a period of 4 weeks. Week 17 6mg daily, Week 18 4mg, Week 19 2mg, and at Week 20 they will no longer take perampanel. (
- History and physical exam, including KPS and a full neurologic assessment, with collection of seizure log (subjects will keep a seizure log throughout the study)
- Toxicity assessment using CTCAE v.4 guidelines
- CBC with diff
- CMP
- Quality of life measurements and neurocognitive testing

Week 24 assessments- End of Treatment) (+ 1 week)

- History and physical exam, including KPS and a full neurologic assessment, with collection of seizure log (subjects will keep a seizure log throughout the study)
- Toxicity assessment using CTCAE v.4 guidelines
- CBC with diff
- CMP
- Quality of life measurements and neurocognitive testing
- Toxicity assessment using CTCAE v.4 guidelines (continuous throughout study)

10.4 End of Treatment

The assessments obtained at the end of Week 24 will serve as the End of Treatment visit, unless the subject withdraws early. If a subject withdraws from the study early, they will be asked to complete the study tests or procedures listed as End of Treatment.

10.5 Follow-up Period

There is no additional follow-up period beyond 24 weeks.

10.6 End of Study

The study will be considered complete once enrollment has been met, procedures on all subjects have been conducted, and data analysis is concluded. The study may also be terminated early for any reason by the PI-sponsor. In order to terminate the study with the Duke IRB, all data extraction and analysis must be complete.

Therefore, if any articles for publication are derived from the current study, they must be submitted and accepted with no further need for additional data extraction or analysis prior to termination with the IRB.

Subjects that are lost to follow-up will be documented in the patient record and in the Excel database.

10.7 Early Withdrawal of Subject(s)

10.7.1 Criteria for Early Withdrawal

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Pregnancy
- Upon request of the subject
- If, in the investigator's medical judgment, further participation would be injurious to the subject's health or wellbeing
- Development of intolerable symptoms
- Non-compliance of the subject
- Development of any exclusion criteria

10.7.2 Follow-up Requirements for Early Withdrawal

If a subject voluntarily withdraws from the study prematurely, they will be asked to complete the tests/procedures that would have been conducted at their next scheduled visit.

10.7.3 Replacement of Early Withdrawal(s)

Not applicable.

10.8 Study Assessments

10.8.1 Medical History

Standard medical history, including concomitant medications, will be obtained and documented per institutional guidelines.

10.8.2 Physical and Neurological Exam

Standard physical exam and neurological assessment will be conducted and documented per institutional and PRTBTC guidelines.

10.8.3 Laboratory Assessments

The timing of laboratory assessments that will be obtained during the course of the study is given in Section 10. A list for each evaluation and what they include is below.

- CBC with differential (hematocrit, hemoglobin, platelet count, white blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, NRBC %, NRBC CT, RDW-CV, absolute lymphocyte count, percent lymphocytes, percent monocytes, percent neutrophils, percent eosinophils, percent basophils, absolute monocyte count, absolute neutrophil count, absolute eosinophil count, absolute basophil count, red blood cell count)
- CMP (albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, total protein, calcium, potassium, sodium, carbon dioxide creatinine, urea nitrogen, glucose, chloride)
- Beta-HCG, if applicable, within 48 hours prior to start of study treatment

10.8.4 Quality of Life and Neurocognitive Assessments

Patient-reported Quality of Life (QoL) outcomes will be assessed using the following standardized and validated questionnaires.

- Functional Assessment of Cancer Therapy-Brain (FACT-BR) scale (version 4), which contains subscales for physical (7-items), functional (7-items), emotional (6-items), and social/family (7-items) well-being, as well as a 23-item brain cancer subscale (BCS) that assesses symptoms commonly reported by brain cancer patients¹⁶
- Functional Assessment of Cancer Therapy-Fatigue (FACT-Fatigue) subscale, version 4¹⁸
- Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) subscale, version 3, which includes subscales for perceived cognitive abilities (9 items) and impact on quality of life (4 items)¹⁹
- Beck depression inventory (BDI), revised version (BDI-II), which contains 21 questions regarding mood symptoms (multiple choice and self-reported). Scores range from 0 (no depression) to 63 (severe depression).²⁰

Neurocognitive testing will include the performance on the following testing using a computerized battery CNS Vital Signs®.²¹ This battery consists of seven tests that measure verbal and visual memory, finger tapping, symbol digit coding, the Stroop Test, a test of shifting attention, continuous performance test. Verbal memory test will assess verbal learning, memory for words, immediate recall, and delayed recall. Visual memory tests will assess visual learning, memory for geometric shapes, immediate recall, and delayed recall. Finger tapping test will assess motor speed and fine motor control. Symbol digit coding test will evaluate complex attention, visual-perceptual speed, and information processing speed. Stroop Test will assess executive function, simple and choice reaction time, speed-accuracy trade-off, information processing speed, and inhibition/disinhibition. Shifting attention test will assess executive function, reaction time, and information processing speed. Continuous performance test will assess sustained attention and choice reaction time. Normative data is available for this testing through CNS Vital Signs® and patients' performance will be compared to this normative data.

Patient demographics, disease history, and concomitant medications will be obtained for all study participants.

References for these standardized tests are provided in Section 15.

10.8.5 Correlative Assessments

Not applicable.

11 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. PI will review and sign off on all adverse events and problems as they occur and will report them to the IRB in accordance with HRPP policies. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of perampanel, whether or not related to use of the perampanel. Abnormal

laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

From the time the subject starts the first dose of perampanel through the End of Study visit (as defined in Section 10.6), all AEs must be recorded in the subject medical record and adverse events case report form.

AEs will be assessed according to the CTCAE version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug
- Probably: The AE is likely related to the study drug
- Possible: The AE may be related to the study drug
- Unlikely: The AE is doubtfully related to the study drug
- Unrelated: The AE is clearly NOT related to the study drug

11.1.1 Reporting of AEs

Eisai should be notified of all treatment-related adverse events on a regular basis (to be agreed upon by the study team and Eisai).

11.2 Serious Adverse Events

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions.

11.2.1 Reporting of SAEs

Only adverse events that the Duke Sponsor-Investigator determines to be serious, unanticipated, and related or possibly/probably (i.e. more likely than not) related to the research must be reported to the Duke IRB. Those adverse events will be submitted in the electronic IRB (eIRB) system, according the following guidelines:

- Report within 24 hours of learning about any subject's death that was unanticipated and more likely related to the research than unrelated;
- Report within 5 business days of learning about any serious, unanticipated, and related or possibly/probably related adverse event;
- Report within 10 business day of learning about any other unanticipated problem or event that was more likely related to the research than unrelated.

If an IND is held, the Sponsor-Investigator must report to the FDA, in an IND safety report, any suspected adverse reaction that is both serious and unexpected. Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction (i.e. there is a reasonable possibility that the drug caused the adverse event)
- Serious
- Unexpected

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The Sponsor-Investigator is required to report to the FDA all IND Safety reports in writing within 15 days (7 days for unexpected fatal or life-threatening suspected adverse reaction). The FDA Form 3500A can be found on the FDA website, www.fda.gov. All other adverse events will be reported to the FDA in the Annual Report.

All suspected adverse drug reactions (those events where a relationship to perampanel is a reasonable possibility) should be reported within **1 business day** of the investigator's awareness to ESI Safety via the email address below.

SAEs will be reported to:

Safety:

Eisai Medical Affairs

100 Tice Blvd.

Woodcliff Lake, NJ 07677

Tel: 1-888-274-2378

Fax: -1-732-791-1111

Email: ESI_Safety@eisai.com

11.3 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 12.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

11.4 External Data and Safety Monitoring Board (DSMB)

Not applicable.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or

potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan. Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

12.2 Audits

The Duke School of Medicine Clinical Trials Quality Assurance (CTQA) office may conduct audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the CTQA auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the CTQA auditor(s) in order to discuss findings and any relevant issues.

CTQA audits are designed to protect the rights and well-being of human research subjects. CTQA audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

CTQA audits examine research studies/clinical trials methodology, processes and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

12.3 Data Management and Processing

12.3.1 Study Documentation

Study documentation includes but is not limited to source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory

bodies/committees, and regulatory documents that can be found in the DCI-mandated “Regulatory Binder,” which includes but is not limited to signed protocol and amendments, approved informed consent forms, FDA Form 1572, and CAP and CLIA laboratory certifications.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' logs or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

12.3.2 Primary Data Collection Document

The Excel spreadsheet will be the primary data collection document for the study. The spreadsheet will be updated in a timely manner following acquisition of new source data. Only the PI, the study coordinator, the data management team, and the clinical trials manager are permitted to make entries, changes, or corrections in the spreadsheet.

12.3.3 Data Management Procedures and Data Verification

Users of the Excel spreadsheet will have access based on their specific roles in the protocol, i.e. the PI, the study coordinator, the data management team, and the clinical trials manager.

The data management team and the statistical team will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The spreadsheet will be reviewed and discussed prior to spreadsheet closure, and will be closed only after resolution of all remaining queries. A record will be kept of all subsequent changes to the data.

12.3.4 Coding

All medical terms will be coded using CTCAE v.4.0, which has been harmonized to MedDRA (Medical Dictionary for Regulatory Activities) coding. Medication will be coded according to the World Health Organization Drug Dictionary.

12.3.5 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

13 STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

13.1 Analysis Sets

As indicated in section 7.4, subject to the availability of data, all patients who receive perampanel treatment will be included in safety analyses. All patients who complete the treatment period of the study will be included in efficacy analyses.

13.2 Patient Demographics and Other Baseline Characteristics

Socio-demographic and clinical characteristics of patients receiving perampanel treatment on this study will be summarized. For categorical variables, frequencies and percentages will be provided. Means with standard deviations or medians/percentiles will summarize non-categorical variables.

13.3 Treatments

The total number of days that the patient received perampanel treatment will be determined for each patient. The percentage of patients who had dose modifications not consistent with the planned dosing during titration, treatment, and tapering will be tabulated by dosing period (i.e. titration, treatment, and tapering).

13.4 Primary Objective

The primary objective of this study is to assess the efficacy of perampanel as an adjunct AED to levetiracetam in patients with primary glioma presenting refractory partial onset seizure activity.

13.4.1 Variable

Efficacy will be assessed by the 50% responder rate, defined as the percentage of patients with a $\geq 50\%$ seizure reduction during the treatment period compared with the seizure frequency before initiation of perampanel. Seizure frequency during treatment perampanel will be computed as the ratio of the total number of seizure episodes while receiving perampanel during the treatment period and the number of days perampanel is administered.

13.4.2 Statistical Hypothesis, Model, and Method of Analysis

As described in Section 3.5 and 13.8, this study has been designed to detect an increase in the 50% responder rate from a benchmark of 20% to 35%. A one-sample binomial test will test this hypothesis at the 0.1 level of significance.

As a related secondary analysis, seizure frequency will be estimated separately for each patient within the titration, treatment, tapering, and follow-up phases of treatment, and the percent reduction in seizure frequency relative to baseline computed. The distribution across patients within each treatment phase in the percent reduction will be described. Depending upon the distribution of these data, means and standard deviations may be used to describe the distribution of percent reduction or quartiles.

13.5 Secondary Objectives

The percentage of patients with unacceptable adverse events that are possibly, probably, or definitely related to perampanel treatment will be calculated. Unacceptable adverse events include all CTCAE Grade 4 or 5 toxicities that are possibly, probably, or definitely related to perampanel, as well as suicidal ideation (any grade) or suicide attempt (Grade 3-5).

13.6 Exploratory Objectives

The effect of perampanel on neurocognition and patient-reported outcomes of quality of life will be explored. Mean changes from baseline in neurocognition and QOL subscales will be computed at each follow-up assessment.

13.7 Interim Analysis

No Interim analyses are planned.

13.8 Sample Size Calculation

The one-arm study will assess the efficacy of perampanel for the treatment of primary brain tumor patients with partial onset seizures. The basis for this assessment is the percentage of patients with a $\geq 50\%$ seizure reduction during the treatment period compared with the seizure frequency before initiation of perampanel (i.e. 50% responder rate).

Several recently conducted randomized studies of patients with partial-onset seizures have reported a 50% responder rate of approximately 20% within the standard treatment arm.²⁻⁴ Steinhoff (2009) also reports a 50% responder rate of approximately 35% within a general population of patients with partial-onset seizures treated with perampanel.²

This study has been designed with 90% power to detect an increase in the 50% responder rate during the treatment period from a benchmark of 20% to 35%. Assuming a type I error rate of 0.1, 61 patients will be required. Based on prior studies the early discontinuation rate was 16%, therefore 71 patients will be enrolled to compensate for patients discontinuing prior to the completion of the treatment period.

14 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

14.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

14.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

14.4 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using Excel, which is housed in an encrypted and password-protected file on a secure network drive. Access to electronic databases (without edit rights) will be limited to the PI, the study coordinator, and the statistical team. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy. Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

14.5 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Section 11 (Sections 11.3 and 11.4 in particular) and Section 12.

14.6 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

14.7 Records Retention

The Principal Investigator will maintain study-related records for the longer of a period of:

- at least two years after the date on which a New Drug Application is approved by the FDA (if an IND is involved)
- at least two years after formal withdrawal of the IND associated with this protocol (if an IND is involved)
- at least six years after study completion (Duke policy)

14.8 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from

situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

The Duke University School of Medicine's Research Integrity Office (RIO) reviews and manages research-related conflicts of interest. The Principal Investigator and Sub-Investigators must report conflicts of interest annually and within 10 days of a change in status, and when applicable, must have a documented management plan that is developed in conjunction with the Duke RIO and approved by the IRB/IEC.

14.9 Registration Procedure

Describe how new subject registration will occur.

15 REFERENCES

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16 APPENDICES

16.1 Appendix A: Cytochrome P450 Drug Interaction Table

Please see the following website for known cytochrome P450 inducers. The website is updated frequently as new information becomes available (Flockhart, 2007)²²:

<http://medicine.iupui.edu/clinpharm/ddis/main-table/>

16.2 Appendix B: Medication and Seizure Log

See attached.