Official Title: **A Phase IV, Prospective, Randomized, Open-Label, Parallel Study Evaluating the Effect of an Adjunctive Anti-Seizure Medication using a Glutaminergic Modulator in Patients with Drug-Resistant Focal Epilepsy and High-Grade Glioma**

NCT04650204

Protocol Version 6.0

23Nov2022

A Phase IV, Prospective, Open-Label, Parallel Study Evaluating the Effect of an Adjunctive Anti-Seizure Medication using a Glutamatergic Modulator in Patients with Focal Epilepsy and High-grade Glioma

Regulatory Sponsor: William O. Tatum, IV, DO FAAN, FACNS
Mayo Clinic Neurology
4500 San Pablo Road
Jacksonville, Florida 32224
904-953-2498

Study Product: Perampanel (PER)

Protocol Number: (IRBe) 19-006286

Initial version: [09/06/2019] Version (2.0)

Current version: [11/23/2022] Version (6.0)

Table of Contents

List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	A Prospective, Open-Label, Parallel Study Evaluating the Effect of an Adjunctive Anti-Seizure Medication using a Glutamatergic Modulator in Patients with Focal Epilepsy and High-Grade Glioma
Running Title	Adjunctive Anti-Seizure Drug (ASD) in Drug-Resistant Focal Epilepsy and high-grade glioma
Protocol Number	19-006286
Phase	IV (investigator-initiated)
Methodology	This is an open-label, parallel study evaluating the effect of PER in patients with biopsy-proven high-grade glioma (grade II and above) and focal epilepsy. Dose ranging will be based on best clinical practice in patients with drug-resistant focal epilepsy.
Overall Study Duration	18 months
Subject Participation Duration	Subject will participate in study procedures for a total duration of 12 months including a 2-to-4-week titration phase, 12-week minimum and 24-week maximum stable treatment phase for interim analysis, and 40 weeks of total treatment time at study termination.
Single or Multi-Site	Single Site
Primary Objectives	To evaluate the efficacy and safety of PER on seizure frequency in adult patients with biopsy-proven high-grade glioma and focal epilepsy compared with alternate ASDs.
Secondary objectives	To assess the progression of biopsy-proven high-grade glioma in patients prescribed a daily dose of 4-8mg of PER for 40 weeks in patients with focal epilepsy when compared with alternate ASD To assess the change in neurocognitive function and brain MRI progression over the course of PER treatment with a daily dose of 4 mg (up to -8mg) in patients with biopsy-proven high-grade glioma and focal epilepsy compared with alternate ASDs. To identify a biomarker-specific response to seizure-reduction in patients treated with PER in patients with a biopsy-proven high-grade glioma (i.e., IDH-mutant vs wildtype).

Number of Subjects	20

Diagnosis and Main Inclusion and Exclusion Criteria	Inclusion Criteria The subject, or the subject's legally acceptable representative is willing to participate in a clinical trial, provides written informed consent, and subject provides written assent, as required by the Mayo Clinic Institutional Review Board (IRB) policy involving human subjects. 1. Subjects that satisfy the following diagnostic criteria: Patients with established clinical diagnoses, of high-grade glioma (WHO class II and above) and epilepsy refractory to at least one ASD, with a seizure frequency of at least 1 seizure per 3-months during baseline. 2. Subjects with body weight of ≥ 40 kg and ≤ 125 kg at screening 3. Adults age 18 and older Exclusion Criteria A. Subject has serious cardiac, respiratory, renal, gastrointestinal, hematologic, or other medical condition as determined by the investigator to potentially interfere with the study B. Subjects with high-grade glioma not following Stupp protocol for treatment of glioblastoma. C. History of status epilepticus in the 6 months prior to screening or a history of seizure clusters progressing to status epilepticus. D. Past medical history of drug and/or alcohol abuse E. Pregnant or breast-feeding F. Subjects treated with PER prior to baseline G. Prior felony conviction disclosed by the patient or previously stated in medical record. H. History of violent behavior I. Clinically significant laboratory abnormality at screening or baseline visits, as determined by the investigators J. Use of an investigational drug or device within 20 days prior to treatment Day 1 K. Repeated radiation therapy for tumor regrowth L. Subjects that plan to undergo tumor resection on or after baseline visit M. Uncontrolled psychiatric disorder at baseline N. Subjects who report active suicidal attempts or suicidality including subjects with a history of suicide attempts or suicidality determined to be

	clinically significant by investigators at screening. O.

Study Product, Dose, Route, Regimen	PER is a noncompetitive AMPA glutamate receptor antagonist. The two phases of the treatment portion of this study include a titration phase and a stable dosing phase. This study will have two treatment arms consisting of PER and alternative ASD arm. The PER arm will begin a titration phase with 2mg PER PO q.d. (may be split to b.i.d.) for one week and increase by 2mg/week until reaching an initial dose of 4mg PO q.d. (q.d. or b.i.d. dosing) is reached. Flexible dosing of PER above 4mg to a maximum of 8 mg daily will be compared to use of alternative ASDs and be guided by best clinical practices with dosing and indication within U.S. FDA guidelines.
Duration of Administration	Participants will be assigned to receive open label PER or an alternate ASD for at least 12 week and up to 40weeks for the remainder of the study. This includes 2-4 weeks of titration and up to 40 weeks of stable dosing. Reduction by 2 mg will be allowed in cases of efficacy if doses greater than 4 mg daily result in non-idiosyncratic side-effects.
Reference therapy	All comparisons will use standard ASDs as the reference therapy using an intent to treat study design for patients initiating or tapering off PER therapy.
Statistical Methodology	Statistical analysis will include Student T-test, Chi-square for categorical differences. An interim analysis will be performed when half of the targeted subjects are enrolled.

1 Introduction

This document is a clinical research protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Does the novelty of Perampanels unique mechanism of action demonstrate anti-seizure efficacy, tumor-cidal activity, and impact progressive impairment in neurocognitive function in patients with high-grade glioma? The major reasons why this study should be conducted include:

1. Seizures commonly occur in 40% to 70% of patients with a primary brain tumor/glioma.[3]
2. PER is FDA approved for adults with focal seizures.[7, 11]

3. PER has novel and unique mechanisms of action that include a primary effect on excitatory amino acids/AMPA.[7,8,11]
4. Glutamate-induced excitotoxicity and disruption of intracellular communication hold a key role in the progression of disease in patients with glioblastoma (altered cysteine-glutamate transport).[5, 10, 11]
5. Glutamate induced over-activity is also suspected to influence high-grade glioma growth.[5, 13]
6. Studies show that isocitrate dehydrogenase 1 (IDH1) mutant gliomas are more likely to cause seizures than IDH1 wild-type gliomas. The IDH1 mutation has been associated with tumorigenesis and has implications relative to differential treatment for primary brain cancer and prognosis.[5]

Because of shared pathways, current anti-seizure drugs (ASDs) may affect treatment of patients with brain tumor, and various antitumor therapies are valuable for seizure management. Mechanisms involving cysteine-glutamine transporters, for example, regulate glutamate release and return through cellular exchange. One explanation for the close link between seizures and glioma evolution are elevated extracellular glutamate levels in the peri-glial and -neuronal space with ensuing over-activity of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-d-aspartate (NMDA) receptors in both conditions. Recent studies point to the role of glutamate in excitotoxic damage resulting in seizures as well as maintenance and invasion of malignant glioma. Blockade of this system could lead to pharmaceutical development that could affect the excitotoxicity of both high-grade glioma and brain-tumor related epilepsy. Human trials of PER demonstrate safety and efficacy as an adjunctive therapy for adult patients with epilepsy. Limited information is available to demonstrate effectiveness in subpopulations associated with excessive glutamatergic stimulation such as brain tumor. PER, a FDA approved AMPA antagonist cleared for clinical use, may have immediate impact in 80,000 patients with brain tumors, and 3.4 million Americans with epilepsy (commonly co-morbid conditions). Anecdotal benefit has been reported in epilepsy patients with primary brain tumor and low dose PER (Vecht et al., 2017). Cognitive decline frequently complicates treatment of patients with high-grade glioma and also in patients with epilepsy impairing overall QoL.

1.2 Investigational Agent

Participants will be assigned to receive open label PER or an alternate ASD for 40 weeks. The route of drug delivery will be orally administered (PO).

1.3 Preclinical Data

Because of shared pathways, current anti-seizure drugs (ASDs) may affect treatment of patients with brain tumor, and various antitumor therapies are valuable for seizure management. Mechanisms involving cysteine-glutamine transporters regulate glutamate release and return through cellular exchange. Blockade of this system could lead to pharmaceutical development that could affect the excitotoxicity of both high-grade glioma and other brain-tumor related epilepsy syndromes. Limited information is available to demonstrate effectiveness in subpopulations associated with excessive glutamatergic stimulation such as brain tumor.

1.4 Clinical Data to Date

Human trials of PER have demonstrated its efficacy as an adjunctive therapy for adult patients with epilepsy. Furthermore, Anecdotal improvements in both seizure frequency and tumor progression have been reported in epilepsy patients with primary brain tumors on low-dose PER (Vecht et al., 2017).

1.5 Dose Rationale

We will follow FDA recommendations for dosing of PER[14]. As such, patients will begin on PER 2 mg PO and increase in weekly intervals of 2 mg/week until reaching minimum dose of at least 4 mg/day and a maximum of 8 mg/day per patient. Alternative ASDs will be instituted according to best clinical practice and without excessive dosing beyond standard doses approved by the U.S. Food and Drug Administration. Participants will be assigned to receive open label PER or an alternate ASD for 40 weeks. The frequency of oral delivery of PER will be every 24 hours but no more frequently than every 12 hours. The route of drug delivery will be orally administered (PO). The otherASD will be chosen and be administered according to prior exposure to ASDs and according to best clinical practice.

1.6 Risks and Benefits

Side effects associated with PER include anxiety, dizziness, headache, irritability, problems with coordination and balance, sleepiness, nausea, and weight gain. Serious side effects observed in clinical trials for patients taking PER include psychiatric and behavioral problems consisting of aggression, hostility, anger, and suicidal thoughts or behavior. In response to these psychiatric and behavioral risks that have been associated with patients beginning PER or taking increased doses of the drug, individuals who disclose history of prior felony conviction or who have violent behavior present in historical review will be excluded from the study. Additionally, any patients with clinically significant suicide risk (e.g., suicide attempt in the past 5 years or active suicidality as judged by the clinician) will be excluded from the study. Patients will be screened and monitored for changes in psychological status and behavior using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), PHQ-9, Columbia-Suicide Severity Rating Scale (C-SSRS), and Quality of Life in Epilepsy Inventory (QOLIE-31) throughout the study. Patients' status will be closely monitored by the physicians throughout the study with the low probability of developing these side effects outweighed by the benefits PER can provide to patients.

2 Study Objectives

Primary Objective

Demonstrate the efficacy and safety of PER on seizure frequency in adult patients with biopsy-proven high-grade glioma and focal Epilepsy compared with alternate ASDs.

Secondary Objective

To assess the change in neurocognitive function and brain MRI progression over the course of PER treatment with a daily dose of 4 mg (up to -8mg) in patients with biopsy-proven high-grade glioma and focal epilepsy compared with alternate ASDs.

To identify a biomarker-specific response to seizure-reduction in patients treated with PER in patients with a biopsy-proven high-grade glioma (i.e., IDH-mutant vs wildtype).

3 Study Design

3.1 General Description

This study is a prospective, open-label trial evaluating the effectiveness of PER on seizure frequency in adult patients with brain-tumor with seizures associated with high-grade glioma. Subjects (n = 20) will be male and female adults with a high-grade glioma recruited from Mayo Clinic in Jacksonville, Florida-William Tatum, DO, (PI). Participants included will have had uncontrolled seizures, on a current regimen of at least 1 ASD manifesting ongoing focal seizures (including focal aware motor, focal impaired

awareness, and focal to bilateral tonic-clonic seizures), with at least 1 seizure/month during a retrospective 2-month baseline, relative to the screening visit.

All patients included in the study will follow STUPP protocol (radiotherapy plus concomitant and adjuvant Temozolomide) for treatment of high-grade glioma in addition to best medical practice of comorbidities, as is standard-of-care[15].

3.2 Number of Subjects

20

3.3 Duration of Participation

12 months

3.4 Primary Endpoints

A. The number of patients with a high-grade glioma who achieve a > 50% reduction in focal seizures with PER 4 mg daily after failing 1 or more ASDs at 3 and 6 months.
1. The overall survival of patients with high-grade glioma treated with PER at 3 months.
2. Decline in neuropsychological function at 6 months.

All comparisons will use intent to treat model for patients initiated or exiting PER therapy. In event of patients not surviving till 12 months, most recent data prior to death will be used for correlation.

3.5 Identification of Source Data

Electronic medical records will be maintained via a RedCAP database for consecutive and prospective collection of data.

Efficacy measures used in the study include: clinical assessments will include serial brain MRI, EEG, anti-seizure drug levels and subject self-assessment at clinical follow-up; Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), assessment for screening of depression PHQ-9;Montreal Outcome Cognitive Assessment (MOCA); Clinical Global Impression of Change (CGIC) score; Columbia –Suicide Severity Rating Scale. Seizure calendars performed at 2 months prior to initiation of therapy or adequate reliable historical baseline, and then monthly during study; and QOLIE-31, (see schedule of events for frequency of assessment).

Anatomic brain MRI with perfusion scanning/gadolinium will be obtained at 3 months and then every 3 months, to examine the correlated progression of brain tumor, or the absence of tumor. Laboratory studies will be employed before and after PER initiation. EEG will be obtained at baseline and at 3 months and 12 months to identify changes in background activity (e.g. diffuse slowing) and epileptiform discharges to correlate with focal seizure presence vs absence. Neuropsychological batteries will determine the presence or absence of significant anxiety, depression or cognitive changes over time and quality of life inventory will be obtained at the beginning, intermediate and end of the trial.

The following source data will be directly recorded on the Case Report Form (CRF):

- A comprehensive History and Physical examination and Neurological examination will occur at the initial screening/baseline.
- Clinical visitation will occur at screening/baseline, 3, 6, and 12 months.

Survey questionnaires will be obtained at baseline, 3, 6, 9, and 12 months. The following source data will not be directly collected in the Case Report Form (CRF), but will be captured in supportive documentation (study source documents, EMR):

- Laboratory studies will be employed at baseline and at each clinical visit after PER initiation.
- Brain tumor tissue will be assessed for the usual molecular markers (i.e., IDH-mutant vs wildtype, MGMT methylation, ARX).
- 12-lead ECG will be obtained at baseline and as clinically indicated
- Anatomic brain MRI with and without gadolinium will be obtained at baseline and follow-up brain MRI at 3 months and 6 months during PER use.
- EEG will be obtained at baseline and at 3 months and 12 months to identify changes in background activity (e.g. diffuse slowing) and epileptiform discharges to correlate with focal seizure presence vs absence.
- Neuropsychological batteries will be obtained at baseline, 3 months, and 6 months to determine the presence or absence of significant neurocognitive decline.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

1. The subject, or the subject's legally acceptable representative is willing to participate in a clinical trial, provides written informed consent, and subject provides written assent, as required by the Mayo Clinic Institutional Review Board (IRB) policy involving human subjects. In the event of subject lacking the capacity or losing the ability to consent, consent will be deferred to subject's legally acceptable representative
2. Subjects that meet the following diagnostic criteria:
   a. Patients with established clinical diagnoses of biopsy-proven high-grade glioma (Grade II or above) and epilepsy refractory to at least 1, drug with a seizure frequency of at least 1 seizure episode per 3-months prior to baseline visit.
3. Subjects with body weight of ≥ 40 kg and ≤ 125 kg at screening.
4. Adults age 18 and older.

4.2 Exclusion Criteria

1. Subject has serious cardiac, respiratory, renal, gastrointestinal, hematologic, or other medical condition as determined by the investigator to potentially interfere with the study
2. Subjects with glioblastoma not following Stupp protocol for treatment of glioblastoma.
3. History of status epilepticus in the 6 months prior to screening or a history of seizure clusters progressing to status epilepticus.
4. Past medical history of drug and/or alcohol abuse
5. Pregnant or breast-feeding
6. Subjects treated with PER prior to baseline
7. Prior felony conviction disclosed by the patient or previously stated in medical record.
8. History of violent behavior
9. Clinically significant laboratory abnormality at screening or baseline visits, as determined by the investigators
10. Use of an investigational drug or device within 20 days prior to treatment Day 1
11. Repeated radiation therapy for tumor regrowth
12. Subjects that plan to undergo tumor resection on or after baseline visit
13. Uncontrolled psychiatric disorder at baseline

14. Subjects who report active suicidal attempts or suicidality including subjects with a history of suicide attempts or suicidality determined to be clinically significant by investigators at screening.

4.3 Subject Recruitment, Enrollment and Screening

Subjects (n = 20), will be male and female adults with a high-grade glioma recruited from Mayo Clinic in Jacksonville, Florida- William Tatum, DO, (PI). 10 subjects will be enrolled into an adjunctive Perampanel and other ASDs group, and 10 subjects will receive only alternative ASDs. There will be a 6-month recruitment period for screening and enrollment. The treating physician will decide, based on best medical practice, which patients are candidates for adjunctive Perampanel and other ASDs, or only alternative ASDs. Patients taking Perampanel will begin their titration phase upon enrollment.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

During this study, medical history will be taken periodically as mentioned in the schedule of events. Physical examinations and neurological examinations will be conducted every study visit except for the 4-week flexible titration (2 mg/week, up to 8mg) visit. Protocol directed screening for adverse events will be performed at each visit.

The Principal and Co-Investigator as well as Study Coordinator are responsible for individual safety monitoring. Stopping or interruption of the study may be necessary if a significant number of study participants develop unexpected clinical flaring or significant worsening that appears temporally linked with PER administration to be used for the indication outlined in this protocol.

The Principal Investigator and/or Investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. For this study, all SAEs or possible UPIRTSOs will be reported to the IRB.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

All study data will be stored in the password protected REDCAP database. Access to the REDCAP database will be limited to the Principal Investigator, Investigators and Statistician. Paper documents, including patient seizure logs/diaries and case report forms, will be kept in a locked cabinet with access available only to the Investigators and Study Coordinator.

The sponsor-investigator will maintain records and essential documents related to the conduct of the study for a period of 2 years after completion of the study. These will include subject case histories and regulatory documents. All study data will be collected and managed using REDCap electronic data capture tools hosted at the Mayo Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

5 Study Drug

5.1 Description

PER is a noncompetitive AMPA glutamate receptor antagonist.

5.2 Treatment Regimen

Patients will begin on PER 2 mg PO and increase in weekly intervals of 2 mg/week until reaching minimum dose of at least 4 mg/day and a maximum of 8 mg/day per patient. Alternative ASDs will be instituted according to best clinical practice and without excessive dosing beyond standard doses approved by the U.S. Food and Drug Administration. Participants will be assigned to receive open label PER or an alternate ASD for 40 weeks. The frequency of oral delivery of PER will be every 24 hours but no more frequently than every 12 hours. The route of drug delivery will be orally administered (PO). The other ASDs will be chosen and be administered according to prior exposure to ASDs and according to best clinical practice.

5.3 Method for Assigning Subjects to Treatment Groups

Participants will be assigned to receive:

Group A: open label arm of adjunctive PER (study drug) for patients with seizures treated with at least 1 ASD administered in escalating divided doses of 2 mg/week to 4 mg daily with flexible dosing to 8 mg/day by 4 weeks. Subjects must undergo forced titration of 2 mg/week and be able to tolerate 4 mg to continue in the study. Concomitant ASD will be utilized according to best clinical practice.

or

Group B: continued open label treatment for patients with seizures treated with at least 1 ASD, as per best medical practice, without the use of PER.

5.4 Preparation and Administration of Study Drug

PER (to be used for the indication outlined in this protocol) will be shipped by Eisai to the Mayo Clinic research pharmacy in Florida. Upon receipt, an inventory will be performed, and a drug receipt log filled out by the person accepting the shipment. Designated study staff will count and verify that the shipment contains all the items noted on the shipping invoice. Any discrepancies, damaged or unusable drug in any given shipment will be documented in the study files. The Investigators must be notified immediately of any discrepancies, damages or unusable products that are received.

5.5 Subject Compliance Monitoring

Anti-seizure drug levels will be evaluated at clinical follow-up (see study schema for frequency of assessment).

5.6 Prior and Concomitant Therapy

Concomitant therapy will allow 0-3 concomitant ASDs. No specific drugs will be disallowed; concomitant ASDs and non-ASDs (e.g. narcotics, benzodiazepines, and barbiturates) will serve as exclusionary therapies when deemed clinically relevant according to best clinical practice.

5.7 Packaging

Study drug will be packaged according to the manufacturer's approval for use by the U.S. FDA.

Bottles containing 20 tablets of 4 mg dosages of PER are anticipated.
Study drug will be shipped separately by subject-specific packages.
The contents of the package will include study drug and associated approved labelling.

5.8 Masking/Blinding of Study

This is an open-label study.

5.9 Receiving, Storage, Dispensing and Return

Study drug will be received by the principal investigator and stored in a secured location. Unused medication will be returned to the study institution and returned to Eisai Pharmaceuticals.

5.9.1 Receipt of Drug Supplies

Perampanel (to be used for the indication outlined in this protocol) will be shipped by Eisai to the Mayo Clinic research pharmacy in Florida. Upon receipt, an inventory will be performed and a drug receipt log filled out by the person accepting the shipment. Designated study staff will count and verify that the shipment contains all the items noted on the shipping invoice. Any discrepancies, damaged or unusable drug in any given shipment will be documented in the study files. The investigators must be notified immediately of any discrepancies, damages or unusable products that are received.

5.9.2 Storage

Perampanel will be stored at Mayo Clinic research pharmacy in Florida. Medication will be stored at room temperature (between 68 and 77º F) with limited exposure to heat, moisture, and light.

5.9.3 Dispensing of Study Drug

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form and signed and dated by the study team.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

6.1 **Visit 1** (Screening)

Informed consent is received, and a review of study inclusion/exclusion criteria is conducted, Medical history and physical examination are performed. Neurological examination is performed. Urine Pregnancy test is performed. Seizure Diary is reviewed.

6.2 **Visit 2** (Baseline)

CBC, CMP, and ASD trough levels are evaluated. An MRI of the brain with volume measurement is completed. An EEG is taken if there has not been one completed within 3 months of the visit.

Neuropsychological baseline visit. Seizure frequency is assessed. PHQ-9, NDDI-E, MOCA, CGIC, C-SSRS and QOLIE-31 are completed.

Screening and Baseline are preferred to be on the same day, but can occur separate days if needed. All screening and baseline events will be completed before Visit 3.

6.3 Visit 3

Seizure frequency is assessed. Seizure Diary is reviewed. PHQ-9, NDDI-E, MOCA, CGIC, C-SSRS and QOLIE-31 are completed. Dispense study drug to participants in Group A (PER arm).

6.4 Visit 4

Seizure frequency is assessed. Seizure Diary is reviewed. PHQ-9, NDDI-E, MOCA, CGIC, C-SSRS and QOLIE-31 are completed. Dispense study drug to participants in Group A (PER arm).

6.5 Visit 5

Seizure frequency is assessed. Seizure Diary is reviewed. CBC, CMP, and ASD trough levels are evaluated. MRI is reviewed. Seizure frequency is assessed. PHQ-9, NDDI-E, MOCA, CGIC, C-SSRS and QOLIE-31 are completed. Dispense study drug to participants in Group A (PER arm).

6.6 Visit 6

Medical history and physical examination are performed. Neurological examination is performed. Seizure Diary is reviewed. Seizure frequency is assessed. PHQ-9, NDDI-E, MOCA, CGIC, C-SSRS and QOLIE-31 are completed. Dispense study drug to participants in Group A (PER arm).

6.7 Visit 7

Visit 7 will be completed by telephone call. Seizure frequency is assessed. Seizure Diary is reviewed. PHQ-9, NDDI-E, CGIC, C-SSRS and QOLIE-31 are completed by asking the participant the questions verbally. The participant will be asked about medical history.

6.8 Visit 8

Seizure frequency is assessed. Seizure Diary is reviewed. Medical history and physical examination are performed. Neurological examination is performed. CBC, CMP, and ASD trough levels are evaluated. An MRI of the brain with volume measurement is completed. An EEG is completed. PHQ-9, NDDI-E, MOCA, CGIC, C-SSRS and QOLIE-31 are completed. Neuropsychological follow-up assessment. Dispense study drug to participants in Group A (PER arm).

6.9 Visit 9

Visit 9 will be complete by telephone call. Seizure Diary is reviewed Seizure frequency is assessed.. PHQ-9, NDDI-E,CGIC, C-SSRS and QOLIE-31 are completed by asking the participant the questions verbally. The participant will be asked about medical history.

6.10 Visit 10

Visit 10 will be complete by telephone call. Seizure frequency is assessed. Seizure Diary is reviewed. PHQ-9, NDDI-E, CGIC, C-SSRS and QOLIE-31 are
completed by asking the participant the questions verbally. The participant will be asked about medical history.

6.11 Visit 11

Seizure frequency is assessed. Seizure Diary is reviewed. Medical history and physical examination are performed. Neurological examination is performed. An MRI of the brain with volume

measurement is completed. An EEG is completed. PHQ-9, NDDI-E, MOCA, CGIC, C-SSRS and QOLIE-31 are completed. Neuropsychological follow-up assessment. Dispense study drug to participants in Group A (PER arm).

6.12 Visit 12

Visit 12 will be complete by telephone call. Seizure Diary is reviewed. Seizure frequency is assessed. PHQ-9, NDDI-E, CGIC, C-SSRS and QOLIE-31 are completed by asking the participant the questions verbally. The participant will be asked about medical history.

6.13 Visit 13

Visit 13 will be complete by telephone call. Seizure frequency is assessed. Seizure Diary is reviewed. PHQ-9, NDDI-E, CGIC, C-SSRS and QOLIE-31 are completed by asking the participant the questions verbally. The participant will be asked about medical history.

6.14 Visit 14

Visit 14 will be complete by telephone call. Seizure frequency is assessed. Seizure Diary is reviewed. PHQ-9, NDDI-E, CGIC, C-SSRS and QOLIE-31 are completed by asking the participant the questions verbally. The participant will be asked about medical history.

6.15 Visit 15

Medical history and examination are performed. Neurological examination is performed. Seizure Diary is reviewed. CBC, CMP, and ASD trough levels are evaluated. An EEG is ordered. MRI is reviewed. Seizure frequency is assessed. PHQ-9, NDDI-E, MOCA, CGIC, C-SSRS and QOLIE-31 are completed. Neuropsychological follow-up assessment.

Schedule of Events[1]

Procedure	Screening & Baseline Visits[4]		Titration Phase[2]				Treatment Phase[2, 8, 9]								
Visit Day	Day 0-6		Day 7	Day 14	Day 21	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180	Day 210	Day 240	Day 270	Day 300
Visit Number	1[4]	2[4]	3	4	5	6	7[8]	8	9[8]	10[8]	11	12[8]	13[8]	14[8]	15
Informed Consent	X														
Inclusion and Exclusion Criteria check[5]	X														
Medical/Surgical History	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological Examination	X					X		X			X				X
Physical Examination	X					X		X			X				X
Clinical Labs[1,3]	X							X			X				X
Historical Anatomical Brain MRI review[7]	X														
Anatomical Brain MRI[1, 7]	X							X			X				X
Historical EEG review[7]	X														
Standard EEG[1, 7]	X							X			X				X
Neuropsychology visit	X							X			X				X
NDDI-E	X		X	X	X	X	X	X	X	X	X	X	X	X	X

PHQ-9	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MOCA	X	X	X	X	X		X			X				X
CGIC	X	X	X	X	X		X			X				X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
QOLIE-31	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test	X													
Dispense Seizure Diary	X	X	X	X	X		X			X				
Seizure Diary Review		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Study Drug[6]		**X**	**X**	**X**	**X**		**X**			**X**				
Study Drug Accountability[6]		X	X	X	X		X			X				X

[1]Clinical assessments (MRI, EEG, clinical labs, and anti-seizure drug levels) performed before or after scheduled follow-up if deemed clinically necessary outside of the study protocol.

[2] ±3-day tolerance window

[3]CMP to include the following blood tests: albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, sodium, total bilirubin and protein, and liver enzymes (alanine aminotransferase, alkaline phosphatase, and aspartate aminotransferase).

[4] Screening and Baseline are preferred to occur consecutively on the same day but, if this is not feasible for the patient, the Baseline Visit procedures can occur any time after screening *and* before Day 7..All screening and baseline results must be available for review prior to dispensing study drug on day 7.

[5] Any development to the patient's history affecting their standing within the inclusion and exclusion criteria will be continually assessed throughout the study.

[6]As needed and only for PER arm.

[7] Baseline MRI and EEG performed only if one has not been performed within three months prior to baseline. , otherwise historical MRI and/or EEG will be reviewed .

[8]Visits 7, 9, 10, 12, 13, and 14 will be completed as Phone Visits (PV).

[9]±7-day tolerance window

7 Statistical Plan

7.1 Sample Size Determination

A sample size of 20 patients is targeted as part of a pilot study to determine feasibility for a larger prospective multi-center trial. The sample size is targeted to achieve adequate enrollment and determine the likelihood of supporting a larger study.

This study is not designed to be powered to determine significance for statistical significance of effectiveness.

7.2 Statistical Methods

Descriptive Statistics

Statistical analysis will include Student T-test, Chi-square for categorical differences. An interim analysis will be performed when half of subjects are enrolled.

Handling of Missing Data

Study data will be collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic. All data requested on the Case Report Form (CRF) will be recorded for each participant. A standardized CRF will be generated by REDCap. For any data query, the Principal Investigator and Investigators will meet to clarify the data queried and make corrections based on consensus. Once the study is completed, the Principal Investigator will randomly select 3 participants and compare the data documented for each on the CRF with what is entered into the REDCap database. If there is any discrepancy, the Principal Investigator and/or Investigators will cross-reference all 20 patients to ensure accuracy.

Primary Hypothesis: We hypothesize that perampanel will lead to a significant reduction in seizure frequency for adult patients with brain tumor-related seizures associated with high-grade glioma.
We will compare seizure frequency before and 3 months after treatment with monotherapy and adjunctive PER and use descriptive statistics to demonstrate differences in responders. A P-value < 0.05 will be used to reflect statistical significance.

Secondary Hypothesis 1: We hypothesize the progression of brain tumor (comparing 4 and 8 mg/d of perampanel) based upon fusion by comparing baseline brain MRI and MRI at 12 months will be less for IDH-mutants.
We hypothesize there will be minimal or no change in neurocognitive function from 0 to 3 months on Montreal Outcome Cognitive Assessment (MOCA; higher scores indicating greater function); and the Clinical Global Impression of Change (CGIC; scores from 1 to 7, with lower scores indicating greater improvement and a score of 4 indicating no change).

Chi-square and Student T-test will be used to measure differences in assessment and change during the study period. A P-value < 0.05 will be considered significant.

Interim Analysis

An interim analysis will be performed when half of subjects are enrolled to assess the safety and efficacy of the study.

7.3 Subject Population(s) for Analysis

Analysis of the protocol-compliant population will be conducted. 3, 6, and 12 month evaluability will be assessed based upon the severity of the glioma disease process associated with brain tumor-related focal seizures and risk of imminent death from high-grade malignant primary brain tumor.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 12 months following the last administration of study treatment.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality will be documented as an adverse event if the conditions of the laboratory are identified as outside the normal expected range for the parameter and in the investigators opinion requires an intervention (e.g., repeat testing, consequences on the disease state, exhibit evidence of organ toxicity, or necessitate dosage reduction, discontinuation of study drug, or additional follow-up).

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should be recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

The sponsor-investigator will report to the sponsor and the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction.

This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

8.4 Stopping Rules

The Principal and Co-Investigators as well as Study Coordinator are responsible for individual safety monitoring. Stopping or interruption of the study may be necessary if a significant number of study participants develop unexpected clinical flaring or significant worsening, as judged by the principal investigator, study coordinator or sponsor, appears temporally linked with Perampanel administration to be used for the indication outlined in this protocol.

The Principal Investigator and/or Investigators will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. For this study, all SAEs or possible UPIRTSOs will be reported to the IRB.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study?
- Who will have access to that information and why?
- Who will use or disclose that information?
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, 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.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

Study data will be collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic. All data requested on the Case Report Form (CRF) will be recorded for each participant. A standardized CRF will be generated by REDCap. For any data query, the Principal Investigator and Investigators will meet to clarify the data queried and make corrections based on consensus.

Data Security and Confidentiality

Study subjects will be consented and evaluated within the Department of Neurology at Mayo Clinic Florida by designated study personnel. All study data will be stored in the password protected REDCAP database. Access to the REDCAP database will be limited to the Principal Investigator, Investigators and Statistician. Paper documents, including patient logs/diaries and case report forms, will be kept in a locked cabinet with access available only to the Investigators and Study Coordinator.

Data Quality Assurance

Once the study is completed, the Principal Investigator will randomly select 3 participants and compare the data documented for each on the CRF with what is entered into the REDCap database.

Data Clarification Process

If there is any discrepancy, the Principal Investigator and/or Investigators will cross-reference all 20 patients to ensure accuracy.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study for a period of 2 years after completion of the study. These will include subject case histories and regulatory documents. All study data will be collected and managed using REDCap electronic data capture tools hosted at the Mayo Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

Subject-specific data and Case Report Forms will be coded using confidential and anonymous ID numbers and subject names and other identifiable information (SS, MRN, DOB) will not appear on any reports, publications, or other disclosures of clinical study outcomes.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717 Whichever is longer.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

DATA AND SAFETY MONITORING PLAN (DSMP)

1. Subject Safety

During this study, medical history will be taken every study visit with the exception of the 3 Month visit. Physical examinations and neurological examinations will be conducted every study visit with the exception of the 4-week flexible titration to 8 mg/d (2 mg q 2 weeks) visit. Protocol directed screening for adverse events will be performed at each visit.

The Principal and Co-Investigator as well as Study Coordinator are responsible for individual safety monitoring. Stopping or interruption of the study may be necessary if a significant number of study participants develop unexpected clinical flaring or significant worsening that appears temporally linked with perampanel administration to be used for the indication outlined in this protocol.

The Principal Investigator and/or Investigator's will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. For this study, all SAEs or possible UPIRTSOs will be reported to the IRB.

2. Data Integrity

Study data will be collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic. All data requested on the Case Report Form (CRF) will be recorded for each participant. A standardized CRF will be generated by REDCap. For any data query, the Principal Investigator and Investigators will meet to clarify the data queried and make corrections based on consensus. Once the study is completed, the Principal Investigator will randomly select 3 participants and compare the data documented for each on the CRF with what is entered into the REDCap database. If there is any discrepancy, the Principal Investigator and/or Investigators will cross-reference all 20 patients to ensure accuracy.

3. Subject Privacy

Study subjects will be consented and evaluated within the Department of Neurology at Mayo Clinic Florida by designated study personnel.

4. Data Confidentiality

All study data will be stored in the password protected REDCAP database. Access to the REDCAP database will be limited to the Principal Investigator, Investigators and Statistician. Paper documents, including patient logs/diaries and case report forms, will be kept in a locked cabinet with access available only to the Investigators and Study Coordinator.

5. Product Accountability

perampanel (to be used for the indication outlined in this protocol) will be shipped by Eisai to the Mayo Clinic research pharmacy in Florida. Upon receipt, an inventory will be performed, and a drug receipt log filled out by the person accepting the shipment. Designated study staff will count and verify that the shipment contains all the items noted on the shipping invoice. Any discrepancies, damaged or unusable drug in any given shipment will be documented in the study files. The Investigators must be notified immediately of any discrepancies, damages or unusable products that are received.

6. Study Documentation

The sponsor-investigator will maintain records and essential documents related to the conduct of the study for a period of 2 years after completion of the study. These will include subject case histories and regulatory documents. All study data will be collected and managed using REDCap electronic data capture tools hosted at the Mayo Clinic. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

7. Study Coordination

The Principle Investigator and study coordinator in Florida shall communicate the procedures and protocols to all participating investigators and track the number of consented subjects on a biweekly basis until accrual targets are met or until the study ends.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

A subject's capacity for consent will be determined by the attending physician and clinical team per standard of care assessments in conjunction with the research staff. Patients will continue to be assessed for their ability to consent and will be re-consented when deemed appropriate.

The study staff will not obtain assent. If a patient lacks the capacity to consent for themselves, they will likely be unable to fully understand the study procedures.

The Legally Authorized Representative (LAR) will be identified by the attending physician and/or case manager in accordance with standard of care practices. Obtaining consent from the LAR will follow the same guidelines as if the patient themselves were being consented.

12 Study Finances

12.1 Funding Source

Feasibility Estimation sent separately and developed by the Office of Sponsored Projects, Mayo Clinic Florida.

13 Publication Plan

Study will be conducted with the intent of the publication of findings in Neurology in 2020 or 2021.

14 References

1.Higgins GA et al. Pharmacological manipulation of mGlu2 receptors influences cognitive performance in the rodent. Neuropharmacology. 2004;46:907–17.
2.Kolker S et al. NMDA receptor activation and respiratory chain complex V inhibition contribute to neurodegeneration in D-2-hydroxyglutaric aciduria. Eur J Neurosci 2002;16:21–8.
3.Neal A et al. Postoperative seizure control in patients with tumor-associated epilepsy. Epilepsia 2016;57:1779–88.
4.Huberfeld G, Vecht CJ. Seizures and gliomas — towards a single therapeutic approach. Nat Rev Neurol 2016;12:204–16.
5.Dang L et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009;462:739–44.
6.Avila EK et al. Seizure control as a new metric in assessing efficacy of tumor treatment in low-grade glioma trials. Neuro Oncol 2017;19:12–21.
7.Rosche et al. Perampanel in the treatment of a patient with glioblastoma multiforme without IDH1 mutation and without MGMT promotor methylation. Fortschr Neurol Psychiatr, 2015; 83(5):286-9.
8.Dang L et al. IDH mutations in cancer and progress toward development of targeted therapeutics. Ann Oncol 2016;27:599–608.
9.Toledo M et al. Epileptic features and survival in glioblastomas presenting with seizures. Epilepsy Res 2017;130:1–6.
10.Chen H et al. Mutant IDH1 and seizures in patients with glioma. Neurology 2017;88:1805–13.
11.Vecht CJ et al. Seizure response to perampanel in drug-resistant epilepsy with gliomas: early observations. J Neurooncol. DOI 10.1007/s11060-017-2473-1.
12.Vecht et al., Seizures and Anticonvulsants in Brain Tumors: Frequency, Mechanisms and Anti-Epileptic Management. Current Pharmaceutical Design, 2017, 23, 1-25.
13.Onco-Epilepsy: more than tumor and seizures. Mayo Clinic Proceedings. 2018 (in press).
14. Faulkner, Michele A. "Perampanel: a new agent for adjunctive treatment of partial seizures." American journal of health-system pharmacy 71.3 (2014): 191-198.
15. Stupp, Roger, et al. "Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma." New England Journal of Medicine 352.10 (2005): 987-996.

15 Attachments

Appendix:

Assessment 1: The NDDI-E is a brief screening tool composed of 6 questions that can be used to rapidly identify patients with clinical depression. The measure removes the potential effect of confounding variables (such as medication effects and cognitive problems) that may influence the diagnosis of depression in patients with epilepsy. A score of greater than 15 has a Cut-off value > 15 for screen failure.

Assessment 2: PHQ-9: a brief depression severity measure

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last 2 *weeks*, how often have you been bothered by any of the following problems? *(use "√" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite —being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
	add columns		+	+
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).	TOTAL:			

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____

A2663B 10-04-2005

PHQ-9 Scores	Severity of depression	Recommended therapeutic interventions
1 à 4	-	none
5 à 9	Mild depression	Follow up, monitoring, repeated administration of the scale
10 à 14	Moderate depression	Treatment plan, advise, follow-up and/or pharmacotherapy
15 à 19	Moderately severe depression	Immediate instauration of pharmacotherapy and/or psychotherapy
20 à 27	Severe depression	Immediate instauration of pharmacotherapy and, if severe impairment in functioning or insufficient treatment response, address rapidly to specialist in psychotherapy and/or collaborative treatment

Assessment 3: Columbia-Suicide Severity Rating Scale (C-SSRS) used for assessment of suicidality during the study by the patient duration/drug exposure to perampanel.

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Past X Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

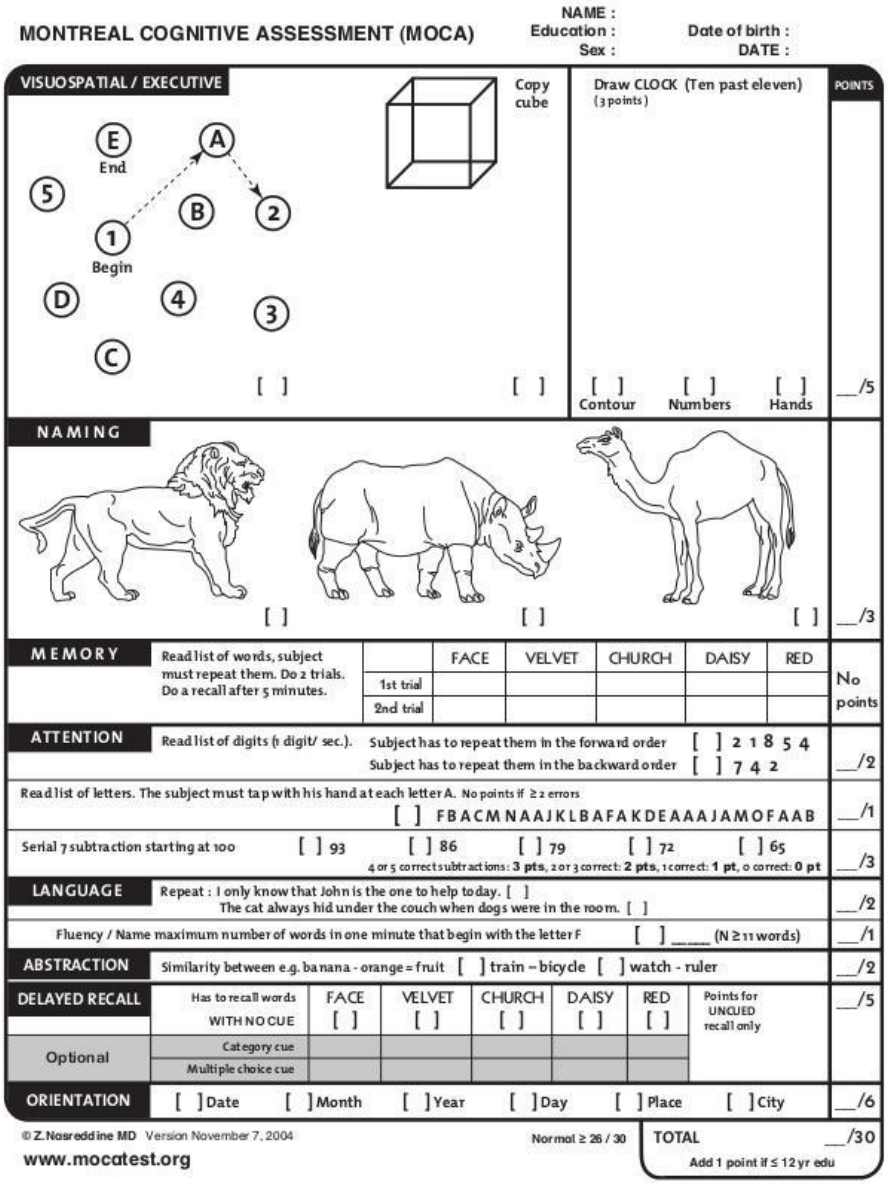
 C-SSRS—Screening (Version 1/14/09) Page 1 of 2

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

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

 C-SSRS—Screening (Version 1/14/09) Page 2 of 2

Assessment 4: MOCA. Score ≥26 is normal; scores <26 indicate mild cognitive impairment and possible dementia



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands __/5

NAMING

[ ] [ ] [ ] __/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4. Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt __/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) __/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

© Z. Nasreddine MD Version November 7, 2004
www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Sensitivity and Specificity (%) MoCA©			
Cut-off	**≥ 26**	**< 26**	**< 26**
Group (n)	Normal controls (90)	Mild Cognitive Impairment (94)	Alzheimer Disease (93)
MoCA©	**87**	**90**	**100**

Assessment 5: Clinician's Global Impression of Change

TABLE 2. CGI-I guidelines
1 = Very much improved—nearly all better; good level of functioning; minimal symptoms; represents a very substantial change
2 = Much improved—notably better with significant reduction of symptoms; increase in the level of functioning but some symptoms remain
3 = Minimally improved—slightly better with little or no clinically meaningful reduction of symptoms. Represents very little change in basic clinical status, level of care, or functional capacity
4 = No change—symptoms remain essentially unchanged
5 = Minimally worse—slightly worse but may not be clinically meaningful; may represent very little change in basic clinical status or functional capacity
6 = Much worse—clinically significant increase in symptoms and diminished functioning
7 = Very much worse—severe exacerbation of symptoms and loss of functioning
Adapted from Spearing MK, Post RM, Leverich GS, et al. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP.*Psychiatry Res* 1997;73(3):159–71.

Assessment 6: QOLIE-

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

Today's Date _____/_____/_____ /
mm dd yy

Name _____

Age _____(years)

INSTRUCTIONS

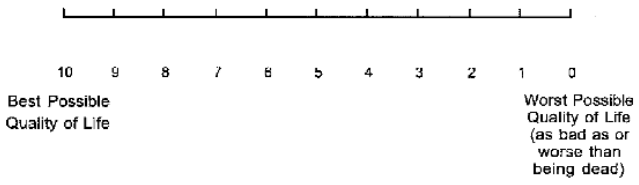
The QOLIE-31 is a survey of health-related quality of life for adults (18 years or older) with epilepsy. Adolescents (ages 11-17 years) should complete the QOLIE-AD-48, designed for that age group. This questionnaire should be completed only by the person who has epilepsy (not a relative or friend) because no one else knows how YOU feel.

There are 31 questions about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3...). If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation on the side of the page. These notes may be useful if you discuss the QOLIE-31 with your doctor. Completing the QOLIE-31 before and after treatment changes may help you and your doctor understand how the changes have affected your life.

This copy of the QOLIE-31 is provided by www.epilepsy.com, your source for epilepsy information, and the QOLIE Development Group. We wish you success in living your life with epilepsy!

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

(Circle one number on the scale below)



31

Cramer JA, Arrigo C, Van Hammee G, Bromfield EB for the N132 Study Group. Comparison between the QOLIE-31 and the derived QOLIE-10 in a clinical trial of levetiracetam. Epilepsy Res 2000; 41: 29-38

INSTITUTION

By: _____
Print: _____
Title: _____

Date: _____