Dana-Farber Cancer Institute

**Office for Human Research Studies**

# Notification of IRB Outcome - Approval

**Date:** July 27, 2020
**To:** Jong Woo Lee
**From:** The Office for Human Research Studies (OHRS)

On 07/27/2020 the IRB reviewed the following protocol:

| | |
|---|---|
| **IRB Protocol Number:** | 20-059 |
| **Type of Review:** | Submission Response for Initial Review Submission Packet |
| **Title:** | Pilot study of perampanel on peritumoral hyperexcitability and seizure control in newly diagnosed high grade glioma |
| **Principal Investigator:** | Lee, Jong Woo |
| **iRIS Reference Number:** | 349473 |
| **Review Process:** | Expedite |
| **Sponsor(s):** | DF/HCC Investigator, Dana-Farber/Harvard Cancer Center, NIH Brain SPORE |
| **Submit Date:** | 07/03/2020 11:13:06 AM EDT |
| **Participating Sites:** | Brigham and Women's Hospital (BWH) |
| **Documents Revised:** | Submission Components Approved |

| Document Type | Version | Date Approved |
|---|---|---|
| Submission-Initial Review Submission Packet | Version 1.1 | |
| Attachment Form-Study Team List | Version 1.0 | |
| Consent Form-Clean Consent Cohort 2 | Version 4.0 | 07/27/2020 |
| Consent Form-Clean Consent Cohort 1 | Version 4.0 | 07/27/2020 |
| Document-Subject Reimbursement Form | Version 1.0 | 07/27/2020 |
| Document-Biomedical Protocol | Version 7.0 | 07/27/2020 |
| Document-Drug Diary | Version 2.0 | 07/27/2020 |
| Document-Seizure diary | Version 1.0 | 07/27/2020 |

**Current state of additional determinations (made previously or on this submission)**:

| | |
|---|---|
| **Risk Level:** | Greater than Minimal Risk under 45 CFR 46 / 21 CFR 56 |
| **Investigational Drug Use:** | IND Exempt as per 21 CFR 312 |
| **Documentation of Consent:** | Written consent in accordance with 45 CFR 46.117/ 21 CFR 50.27 |
| **HIPAA:** | HIPAA Authorization for research approved under 45 CFR 164.508 (a) (1)<br>Partial waiver of HIPAA Authorization for Research approved under 45 CFR164.512 (i) (2) (ii) |

**NCI Protocol #:** N/A

**DF/HCC Protocol #:** 20-059

**TITLE:** Pilot study of perampanel on peritumoral hyperexcitability and seizure control in newly diagnosed high grade glioma


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**Statistician:** N/A

**Study Coordinator:** N/A

**Responsible Research Nurse:** N/A

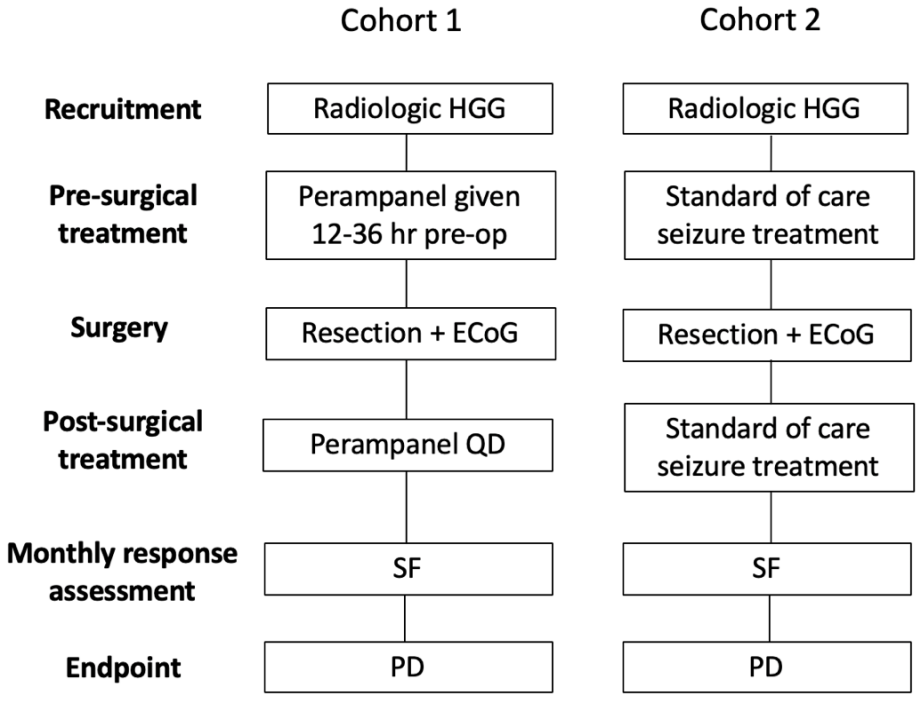
**Responsible Data Manager:** N/A

**NCI-Supplied Agent(s):** N/A
**Other Agent(s):**
Perampanel
NSC # N/A
Eisai Inc.

**Study Exempt from IND Requirements per 21 CFR 312.2(b).**

**SCHEMA**

Cohort 1 will be recruited and treated concurrently with Cohort 2




HGG = high grade glioma
ECoG = electrocorticography
SF = seizure frequency
PD = progressive disease

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# 1. OBJECTIVES

Study Hypothesis #1: Perampanel treatment reduces peritumoral hyperexcitability in newly diagnosed high grade glioma (HGG).

Study Hypothesis #2: Perampanel treatment in newly diagnosed HGG is associated with improvement in seizure control.

## 1 Study Design

This pilot study (Cohort 1) in participants with newly discovered radiologic lesions consistent with HGG evaluates the effect of perampanel on peritumoral hyperexcitability, measured by the rate of high frequency oscillations on intra-operative electrocorticography (ECoG), compared to a contemporary observational control group (Cohort 2) of participants undergoing ECoG and standard peri-operative seizure management. To estimate the effect size of early perampanel treatment on ongoing seizure control, participants in Cohort 1 will be maintained post-operatively on perampanel, adjusted on a clinical basis until evidence of disease progression (or maximum of 12 months), and compared to participants in Cohort 2 receiving standard of care post-operative seizure management.

## 1.1 Primary Objectives

Primary Objective: Measure the effect of perampanel on peritumoral hyperexcitability using intraoperative ECoG at the time of initial glioma resection. We will analyze high frequency oscillations (80-500 Hz) as a biomarker of peritumoral hyperexcitability and epileptogenicity. The rate of high frequency oscillations over 10 minutes of recording in the tumor margins will be compared between perampanel treated participants (Cohort 1) and control participants (Cohort 2).

## 1.2 Secondary Objectives

Secondary Objective: Estimate the clinical effect of perampanel maintenance therapy on seizure control. We will measure seizure-free rates between the time of initial glioma resection and radiographic tumor progression (up to a maximum of 12 months), in participants continued on perampanel post-operatively (Cohort 1) compared to control participants (Cohort 2).

# 2. BACKGROUND

## 2.1 Study Disease(s)

This study evaluates peritumoral hyperexcitability and tumor-associated seizures in HGG, including WHO Grade III anaplastic astrocytoma and WHO Grade IV glioblastoma. Seizures are seen in up to 60% of patients with HGG,[1] and contribute to decreased quality of life.[2] While seizures generally occur earlier in the disease course, up to half of patients with HGG and

glioma-associated epilepsy continue to have uncontrolled seizures despite anti-seizure medications.[3,4] To date, there are no evidence-based guidelines or widely accepted standards of care regarding the use and duration of anti-seizure medications to prevent seizures in this population, or evidence to guide the choice of one anti-seizure medication over another.[5]

Different glioma subtypes have unique propensities for the development of seizures, suggesting that gliomagenesis and epileptogenesis are inter-related, and that variable mechanisms may be involved.[6,7] Among the mechanistic pathways with the most experimental evidence is dysregulation of glutamatergic signaling, whereby excitatory glutamatergic signaling pathways are upregulated in the glioma microenvironment, and contribute to excitotoxicity.[7,8] Preclinical studies demonstrate an increase peritumoral glutamatergic hyperexcitability mediated through multiple mechanisms, including activation of the system $x_c^-$ cystine-glutamate transporter, and AMPA-receptor mediated neuron-glioma synaptic activity.[9,10] Recent evidence indicates that glioma growth is dependent on glutamatergic neuronal activity, mediated by the release of neuroligin-3 and the downstream activation of PI3K-mTOR signaling.[8,11,12] Glutamate release from glioma cells leads to the development of neuronal-glial synaptic connections, hyperexcitability, and further tumor growth in a positive feedback loop. Thus, excessive excitatory signaling appears to be a shared mechanism underlying tumor growth and epileptogenesis, and a promising therapeutic target.

The clinical relevance of peritumoral hyperexcitability in management of glioma-associated epilepsy remains uncertain, however early evidence linking glioma growth with excessive neuronal synaptic activity offers the possibility of targeted therapies with enhanced efficacy.[8,10] Through its anti-glutamatergic actions, the AMPA-receptor antagonist perampanel has been shown to inhibit glioblastoma growth in vitro,[13] and has been associated with radiologic glioma responses in a small clinical case series.[14] In a small series patients with glioma-associated epilepsy refractory to at least two anti-seizure medications, perampanel resulted in seizure freedom in half of cases.[15] Therefore, perampanel treatment may have the potential to inhibit neuronal activity-dependent glioma progression and improve seizure control through reduction of peritumoral hyperexcitability.

### 2.2 IND Agent(s)

N/A

### 2.3 *Other Agent(s)*

Perampanel is a non-competitive AMPA-receptor antagonist, which obtained initial FDA approval in 2012 for the adjunctive treatment of focal and generalized epilepsy, and gained FDA approval in 2017 for use as monotherapy for the treatment of focal epilepsy. In three placebo-controlled trials of perampanel in drug-resistant focal epilepsy, a combined response rate (≥50% seizure reduction) was observed in 19%, 29%, 35%, and 35% of patients treated with placebo, 4mg, 8mg, and 12mg, respectively.[16]

With high bioavailability (~100%) and blood-brain barrier penetration,[17] and long half-life (average 105 hours), effective levels in the brain can be achieved after a single loading dose.

Doses up to 32mg have been used safely in humans, and a median dose of 6mg has been found to terminate status epilepticus after a median of 24 hours.[18] The minimum therapeutic dose is 4mg daily. In placebo-controlled trials, the rate of perampanel discontinuation due to adverse effects in subjects receiving doses of 4mg was 3%, compared to 5% receiving placebo.[16] Given these data, perampanel will be given as a single loading dose of 6mg on the day prior to resection, then continued at 4mg daily. Additional dose adjustments will be made on a clinical basis, as per institutional standards. Dose and schedule modifications will not affect the objectives of this study.

Perampanel is extensively metabolized via primary oxidation (primarily mediated by CYP3A4/5 and to a lesser extent by CYP1A2 and CYP2B6) and sequential glucuronidation. Perampanel is eliminated mostly in the feces (48%) and to a lesser extent in the urine (22%). Moderate and strong CYP3A4 inducers decrease plasma levels of perampanel by approximately 50-67%.[16]

## 2.4 Rationale

Preclinical studies of glioma-associated epilepsy demonstrate an increase in peritumoral glutamatergic hyperexcitability mediated through multiple mechanisms, including activation of the system $x_c^-$ cystine-glutamate transporter,[9,19] and AMPA-receptor mediated neuron-glioma synaptic activity.[10,12] Through its anti-glutamatergic actions, perampanel has demonstrated both anti-tumor and anti-seizure effects in vitro and in vivo.[13,14] In one series of patients with glioma-associated epilepsy, perampanel was associated with a reduction in tumor volume in half of cases, correlated with plasma drug levels.[14] Additionally, objective seizure responses of 75-100% have been reported in small series of patients with drug-resistant glioma-associated epilepsy treated with perampanel after the failure of at least two other anti-seizure medications.[14,15] Thus, perampanel treatment may have the potential to inhibit neuronal activity-dependent glioma progression and improve seizure control through reduction of peritumoral hyperexcitability. Since glioma progression is independently associated with increased seizure frequency,[1,20] this study aims to correlate perampanel use with reduction in peritumoral hyperexcitability at initial diagnosis, and estimate the effect of maintenance therapy on seizure control up to the time of progressive disease.

## 2.5 Correlative Studies Background

Interictal high frequency oscillations (HFOs) measured using intracranial EEG have been previously associated with the seizure onset zone,[21–23] and resection of regions generating HFOs associated with improved seizure outcomes in retrospective analyses of surgical epilepsy series.[24] High frequency activity has also been demonstrated in peritumoral regions in intra-operative ECoG recordings,[10,25] representing a promising biomarker of peritumoral epileptogenicity. As described in Section 1, the primary objective is a correlative study testing the hypothesis that perampanel will reduce peritumoral HFOs through a mechanism of targeting excessive peritumoral glutamatergic activity.

Glioma-related excitotoxicity is primarily attributed to excessive glutamate release and impaired re-uptake in the peritumoral environment.[26] In-vivo microdialysis in the tumor margins of high

grade gliomas have demonstrated a metabolic profile involving decreases in glucose, and increases in lactate/pyruvate ratios, glutamate, and glycerol concentrations.[27] However, whether specific electrophysiologic signatures reflect these local metabolic tissue changes remains uncertain. This protocol involves a correlative tissue analysis of peritumoral metabolites and principal excitatory/inhibitory neurotransmitters to define excitotoxic changes in relation to electrophysiologic excitability. Molecular analysis will be performed using a mass spectrometry method that bypasses the needs for systemic injections of molecular probes required for traditional molecular imaging methods.

Mass spectrometry is a well-established analytical technique used to identify and characterize molecules based upon their accurate mass. More specifically here, we will use Matrix Assisted Laser Desorption Ionization (MALDI) mass spectrometry imaging (MSI) to directly map the distribution of metabolites and neurotransmitters in tissue sections with correlation to histopathology evaluation of the tissue.

## 3. PARTICIPANT SELECTION

### 3.1 Eligibility Criteria

3.1.1 Participants must have radiologic evidence of anaplastic astrocytoma or glioblastoma multiforme within 14 days of enrollment.

3.1.2 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension as ≥10 mm (≥1 cm) with CT or MRI. See Section 11 (Measurement of Effect) for the evaluation of measurable disease.

3.1.3 Age ≥18 years.

3.1.4 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.5 Participants must have adequate organ and marrow function as defined below:

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin ≤ institutional upper limit of normal (ULN)
- AST(SGOT)/ALT(SGPT) ≤3 × institutional ULN
- glomerular filtration rate (GFR) ≥ 30 mL/min/1.73 $m^2$ (see Appendix B)

3.1.6 Human immunodeficiency virus (HIV)-infected participants on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.7 For participants with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.8 Participants with a history of hepatitis C virus (HCV) infection must have been treated

and cured. For participants with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.9 Participants with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.10 Participants with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, participants should be class 2B or better.

3.1.11 The effects of perampanel on the developing human fetus are unknown. For this reason and because some anti-seizure medications are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

**3.2 Exclusion Criteria**

3.2.1 Participants with brain metastases due to confounding effects on the study objectives.

3.2.2 History of allergic reactions attributed to compounds of similar chemical or biologic composition to perampanel.

3.2.3 Participants receiving any medications or substances that are moderate or strong inducers of CYP3A4 are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the participant is considering a new over-the-counter medicine or herbal product.

3.2.4 Participants with uncontrolled intercurrent illness.

3.2.5 Participants with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Pregnant women are excluded from this study because perampanel is an anti-seizure agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with perampanel, breastfeeding should be discontinued if the mother is treated with perampanel.

3.2.7 Participants with a history of suicide attempt or current active suicidal ideation with intent as defined by Columbia Suicide Severity Rating Scale (C-SSRS) type 4-5, due to the potential for suicidal ideation with the use of all anti-seizure medications.

3.2.8 Participants who are unable to swallow pills.

3.2.9 Participants with tumor associated seizures greater than one month before planned surgery.

3.2.10 Participants currently receiving treatment with more than one anti-seizure medication.

### 3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

## 4 REGISTRATION PROCEDURES

In order to maximize enrollment into the pilot study over a short time, and given the difficulty in recruiting participants within a narrow pre-operative time window, we will perform concurrent recruitment into the single arm pilot group (Cohort 1) and a contemporary observational control group (Cohort 2). Eligible participants will be informed and provided the consent forms for both study groups, and those who have no preference will be enrolled in the cohort with the smaller current enrollment, while those who express a preference will be enrolled into the cohort of their preference (up to a maximum enrollment of 10 per cohort). This will enable eligible participants to be enrolled who decline to be randomized. We do not anticipate a systemic bias in endpoints using this method of enrollment, as potentially confounding factors (described in Section 13) are not expected to influence enrollment preferences, although we cannot completely exclude it.

### 4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention.

Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off study in the CTMS (OnCore) with an appropriate date and reason entered.

### 4.1 **Registration Process for DF/HCC Institutions**

Applicable DF/HCC policy (REGIST-101) must be followed.

### 4.2 **General Guidelines for Other Investigative Sites**

N/A

### 4.3 **Registration Process for Other Investigative Sites**

N/A

## 5. TREATMENT PLAN

### 5.1. Treatment Regimen

Perampanel will be given every day until meeting the study endpoint(s). Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. Other anti-seizure medication(s) may be administered during perampanel maintenance therapy as clinically indicated.

Cohort 1
Participants who are already receiving an anti-seizure medication pre-operatively for treatment of tumor-associated seizures will receive their last dose at least 36 hours before scheduled surgery start-time, and then will be switched to perampanel. The loading dose of perampanel will be 6mg by mouth, given on the day prior to surgery (12-36 hours before scheduled start time), followed by a maintenance dose of 4mg by mouth once a day. Participants will be requested to maintain a drug diary of each dose of medication. The drug diary will be returned to clinic staff at the end of each month.

| Study day | Perampanel dose |
|---|---|
| Day 1 (load) | 6mg |
| Day 2+ (maintenance) | 4mg |

Cohort 2
Perioperative and post-operative seizure management will be performed by the primary treating physician(s) according to institutional standards.

## 5.2. Pre-Treatment Criteria

N/A

## 5.3. Agent Administration

5.3.1. *CTEP and/or CIP IND Agent(s), or other IND agent*

N/A

*5.3.2. Other Agent(s)*

Perampanel:
Each perampanel dose will be a single tablet taken by mouth once a day. A loading dose of 6mg will be administered 12-36 hours prior to planned surgery start time. Maintenance dosing of 4mg will start 24 hours after the loading dose, and continued daily. Perampanel may be administered with or without food. It should not be crushed, chewed, or dissolved. Doses should be retaken if missed or vomited. There is no specific observation period required. There are no specific caregiver precautions.

*5.3.3. Other Modality(ies) or Procedures*

Electrocorticography (ECoG):
Intraoperative electrocorticography (ECoG) will be performed for 10 minutes using an Xltek machine (Natus Medical Inc, Pleasanton, CA), sampled at 1000 Hz per channel, with a subdural 4x5 electrode grid overlying the tumor margins, according to institutional clinical protocols. At least 10 minutes prior to ECoG, inhaled anesthetics and propofol infusion will be stopped, as per standard institutional practices. Subsequent tumor resection will be performed at the discretion of the neurosurgeon, and high frequency activity will be analyzed independently post-operatively (see Section 9.1).

5.3.4. *Investigational Imaging Agent Administration*

N/A

## 5.4. General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of perampanel with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix C presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

## 5.5. Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for 12 months or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the study protocol when any of these criteria apply. The reason for removal from protocol, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant. Perampanel may be continued on a clinical basis by the primary treating physician. If the participant is taken off protocol for active suicidal ideation with intent (defined by the Columbia Suicide Severity Rating Scale Type 4-5), the Principal Investigator will arrange for immediate psychiatric evaluation.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

### 5.6. Duration of Follow Up

Participants will be followed as clinically indicated after removal from protocol or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. After completion of the study, if the treating neurologist cannot be contacted or the participant no longer wishes to see their treating neurologist, the principal investigator will help the participant to transition care to a different treating neurologist and will follow them clinically until then.

### 5.7. Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Disease progression
- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

## 6. DOSING DELAYS/DOSE MODIFICATIONS

Perampanel dose modifications are permitted as clinically indicated to optimize seizure control and minimize adverse effects. Dose adjustment may be performed by the primary treating neurologist and/or study investigators. For any adjustment, the Principal Investigator, Dr. Lee, will be notified. A maximum daily maintenance dose for this study will be 8mg.

At the completion of the study, if perampanel is not clinically indicated and/or planned to be withdrawn, the daily dose will be tapered down by 2mg per week to the minimum therapeutic dose of 4mg, then stopped. If perampanel is being discontinued for lack of seizure efficacy, an alternative anti-seizure medication chosen at the discretion of the primary treating neurologist will be started and titrated to a therapeutic dose, after which perampanel will be tapered off as above. If the participant experiences a serious adverse event attributed to perampanel, the drug may be stopped immediately if, at discretion of the Principal Investigator, the benefits outweigh the risks.

## 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

### 7.1. Adverse Event List

#### 7.1.1. Adverse Event List for Perampanel

Based on pooled adverse events seen in ≥2% of patients and more frequently than placebo in controlled trials of perampanel at a dose of 4mg for drug-resistant focal epilepsy (N=172),[16] the most likely adverse events to be seen in this study include:
- dizziness
- somnolence
- irritability
- fatigue
- vertigo
- anxiety
- weight gain
- oropharyngeal pain

Participants will be referred to the package insert(s) for the comprehensive list of

adverse events.

## 7.2. Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

## 7.3. Adverse Event Reporting

7.3.1. In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

7.3.2. Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3. DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.3.4. Protocol-Specific Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

Events not considered to be serious adverse events for this protocol are:
-Hospitalization for seizure
-Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission

### 7.4. Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

### 7.5. Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

## 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the agent administered in this study can be found in Section 7.1.

### 8.1. Perampanel

#### 8.1.1. Description

The chemical name of the active ingredient is 2-(1′,6′-dihydro-6′-oxo-1′-phenyl[2,3′-bipyridin]-5′-yl)-benzonitrile, hydrate (4:3). The molecular formula is C23H15N3O • 3⁄4H2O and the molecular weight is 362.90 (349.39 for anhydrous perampanel).

Perampanel is rapidly and completely absorbed after oral administration with negligible first-pass metabolism. Median time to reach peak concentration ($t_{max}$) ranged from 0.5 to 2.5 hours under fasted condition. Co-administration of perampanel tablet with a high fat meal had no impact on the total exposure ($AUC_{0\text{-}inf}$) of perampanel and reduced the peak plasma concentration ($C_{max}$) of perampanel by 11%-40%. The $t_{max}$ was delayed by approximately 1-3 hours in fed state compared to that under fasted conditions.

Data from in vitro studies indicate that, in the concentration range of 20 to 2000 ng/mL, perampanel is approximately 95- 96% bound to plasma proteins, mainly bound to albumin and α1-acid glycoprotein. Blood to plasma ratio of perampanel is 0.55-0.59.

Perampanel is extensively metabolized via primary oxidation and sequential glucuronidation. Oxidative metabolism is primarily mediated by CYP3A4/5 and to a lesser extent by CYP1A2 and CYP2B6, based on results of in vitro studies using recombinant human CYPs and human liver microsomes. Other CYP enzymes may also

be involved.

Following administration of radiolabeled perampanel, unchanged perampanel accounted for 74-80% of total radioactivity in systemic circulation, whereas only trace amounts of individual perampanel metabolites were detected in plasma.

Following administration of a radiolabeled perampanel tablet dose to 8 healthy elderly subjects, 22% of administered radioactivity was recovered in the urine and 48% in the feces. In urine and feces, recovered radioactivity was primarily composed of a mixture of oxidative and conjugated metabolites. Population pharmacokinetic analysis of pooled data from 19 Phase 1 studies reported that $t_{1/2}$ of perampanel was 105 hours on average. Apparent clearance of perampanel in healthy subjects and patients was approximately 12 mL/min.

The concomitant use of known moderate and strong CYP3A4 inducers including carbamazepine, phenytoin, or oxcarbazepine with FYCOMPA decreased the plasma levels of perampanel by approximately 50-67%.

Perampanel $C_{max}$ and $AUC_{0\text{-}72h}$ were not altered when a single 6-mg dose of perampanel tablet was administered to healthy female subjects following a 21-day course of oral contraceptives containing ethinylestradiol 30 µg and levonorgestrel 150 µg. Co-administration of perampanel 4 mg tablet once daily with an oral contraceptive containing ethinylestradiol 30 µg and levonorgestrel 150 µg for 21 days did not alter $C_{max}$ or $AUC_{0\text{-}24h}$ of either ethinylestradiol or levonorgestrel in healthy female subjects. In another study, a single dose of the oral contraceptive was administered following 21-day once daily dosing of perampanel 12 mg or 8 mg tablets in healthy females. Perampanel at 12 mg did not alter $AUC_{0\text{-}24h}$ of ethinylestradiol but decreased its $C_{max}$ by 18%, and also decreased $C_{max}$ and $AUC_{0\text{-}24h}$ of levonorgestrel by 42% and 40%, respectively. Perampanel at 8 mg did not have significant effect on $C_{max}$ or $AUC_{0\text{-}24h}$ of either ethinylestradiol or levonorgestrel, with a decrease in AUC0-24h of levonorgestrel (9% on average).

8.1.2. **Form**

Perampanel drug product will be as follows:
-4mg tablet, red, round, debossed with “4” on one side and “Є 277” on the other
-6mg tablet, pink, round, debossed with “6” on one side and “Є 294” on the other
-8mg tablet, purple, round, debossed with “8” on one side and “Є 295” on the other

Tablets contain the following inactive ingredients: lactose monohydrate, low substituted hydroxypropyl cellulose, povidone, microcrystalline cellulose, magnesium stearate, hypromellose, polyethylene glycol, talc, titanium dioxide, red ferric oxide (4mg, 6mg, 8mg), black ferric oxide (8mg).

8.1.3. **Storage and Stability**

Tablets: store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

8.1.4. **Compatibility**

There are no known compatibility issues.

8.1.5. **Handling**

Routine handling is recommended.

8.1.6. **Availability**

Perampanel is commercially available and manufactured by Eisai Inc; it will be provided free of charge for this study by Eisai.

8.1.7. **Preparation**

No preparation is required.

8.1.8. **Administration**

Perampanel will be administered by mouth once a day.

8.1.9. **Ordering**

Investigators will order and acquire perampanel directly from Eisai Inc.

8.1.10. **Accountability**

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11. **Destruction and Return**

Perampanel will be destroyed on site or returned to the research pharmacy according to institutional policies, and documented in the Drug Accountability Record Form.

## 9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

## 9.1. Electrocorticography

As the primary outcome for this study, HFOs will be measured in intra-operative ECoG recordings from all participants in Cohort 1 and Cohort 2. ECoG data will be analyzed post-operatively. HFOs will be visually identified after filtering (FIR, order 500, bandpass 80-500 Hz) using Persyst Insight (Persyst Development Corp, Solana Beach, CA). The rate of HFOs per channel per subject will measured for analysis.

ECoG is a standard clinical procedure utilized for epilepsy and brain tumor surgery. There will be no deviations from standard institutional protocols for this study. The investigators are experienced in the performance of this procedure and analysis of ECoG data. The use of ECoG is expected to increase the length of surgery by 15-20 minutes.

There is a low chance (3-4%) that ECoG may reveal subclinical electrographic seizures or highly epileptiform activity that would not be otherwise identified,[31] and would allow for immediate treatment to decrease the risk of intra-operative brain injury.

## 9.2. Laboratory Correlative Studies

### 9.2.1. Intraoperative Stereotactic Molecular Imaging

This protocol involves an optional ancillary/exploratory tissue study involving mass spectrometry analysis and histopathology evaluation. The aim of this correlative analysis is to measure the metabolic profile, neurotransmitter profile, and study drug tissue distribution in resected tissue specimens. Although glutamatergic excitotoxicity is thought to contribute to tissue necrosis,[26] the relationship between excitotoxic tissue injury and electrophysiologic biomarkers in human glioma is poorly understood. We hypothesize that peritumoral hyperexcitability and excitotoxic metabolic profiles will be correlated with the tissue distribution and concentration of anti-seizure medications in the peritumoral microenvironment. We propose to study the correlation between ECoG high frequency activity, histopathology, drug tissue distribution, neurotransmitter concentrations, and metabolic profile from surgical specimens.

This analysis of surgical tissue will be performed in collaboration with Dr. Nathalie Agar, using methods according to Partners IRB protocol 2011P002387. Identification of drug and metabolites in surgical tissue specimens will be performed with MALDI MSI and a neuronavigation system to allow the subsequent infusion of molecular information into the MRI. This technique has been validated by Dr. Agar and collaborators for detection of tumor metabolites,[32] tumor subtype classification,[33] and therapeutic drug distribution.[34] Given that multiple samples will be analyzed per participant, this study enrolling up to 20 participants across cohorts will be sufficient to demonstrate interpretable and meaningful results.

#### 9.2.1.1. Collection of Specimens

No changes will be made to the routine clinical care of patients in this study. All aspects of the surgical management including preoperative and postoperative care will be carried out per the standard of care. Specimens will be collected for the study during tumor resection. The study

will not affect the manner or quantity of tissue removed. In addition to the bulk tumor specimen as routinely sent, numerous small specimens will be collected during the resection using tumor forceps at sampling positions registered to pre-operative MRI images using a navigation system (General Electric Instatrak or BrainLab Vector Vision). All specimens will be sent to the BWH Tissue Biorepository. When the Tissue Biorepository has confirmed that enough tissue has been collected to make a diagnosis, specimens will be made available MALDI MSI.

9.2.1.2. Handling of Specimens

Specimens for correlative analysis will be banked by the SPORE Pathology Core (Directors: David Louis MD, Keith Ligon MD, PhD). A dedicated pathology banking assistant will track and collect tissue for fresh, frozen, and culture analysis. The tissue will be quality control screened by a banking Neuropathologist Staff and scored for percentage tumor composition, necrosis, inflammation, and normal brain tissue content. Specimens will be analyzed by MALDI MSI (Bruker Daltonics), and associated with histopathology for tumor cell prevalence and select histological features. Microscopy images of standard histopathology staining will be co-registered with mass spectrometry images of a given tissue section to resolve the molecular signature of distinct histology features such as cell density, necrosis, and vascularization. The histopathological validation will be correlated to radiology and clinical information via Mirax Digital Slide Desktop (MDSD) database (Zeiss). As part of this study, we will study the differences in the molecules that occur within different regions of the tumor (e.g. at the boundaries between tumor and normal tissues). Metabolic profiling will involve analysis of tissue pH, lactate, pyruvate, and lipid composition. Neurotransmitter profiling will involve analysis of glutamate, glutamine, and GABA composition. Drug distribution will be performed for perampanel and levetiracetam.

9.2.1.3. Shipping of Specimens

Specimens will not be shipped off site.

9.2.1.4. Sites Performing Correlative Study

Tissue analysis will be performed at BWH by Nathalie Agar. All correlative analyses will be performed at BWH.

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans must be done $\leq$2 weeks prior to the start of therapy. If the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours of assessment. Study visits will be performed at monthly intervals by clinic or phone interviews. Clinical response will be evaluated at each study visit. Adverse events will be assessed with each study visit at minimum, and more frequently as clinically indicated.

| | Baseline | Pre-surgery | During surgery | Post-surgery maintenance | Off Study[d] |
|---|---|---|---|---|---|
| Perampanel administration (Cohort 1) | | A | | Every day | |
| Electrocorticography | | | X | | |
| Tumor biopsy | | | X | | |
| Informed consent | X | | | | |
| Demographics | X | | | | |
| Medical history | X | | | | |
| Concurrent Medications | X---------- | | | | ----------X |
| Physical exam | X | | | | |
| Vital signs | X | | | | |
| Height | X | | | | |
| Weight | X | | | | |
| Performance status | X | | | Every month | |
| B-HCG | X[b] | | | | |
| Serum chemistry[a] | X | | | | |
| Seizure Frequency | X | | | Every month | |
| Tumor Measurements | X | | | X[c] | |
| Radiologic Evaluation | X | | | X[c] | |
| Adverse Event Evaluation | | X---------- | | | ----------X[e] |

A: Perampanel: Dose as assigned
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential).
c: At discretion of primary treating neuro-oncologist.
d: Perampanel may be continued on a clinical basis off protocol.
e: Adverse events will be evaluated up to 30 days after study completion.

## 11. MEASUREMENT OF EFFECT

### 11.1. Antitumor Effect

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed according to institutional standards at the discretion of the primary treating neuro-oncologist. For the purposes of this study, participants will be re-evaluated after every MRI for the study endpoint of progressive disease or death, defined by the criteria proposed by the Response Assessment in Neuro-Oncology (RANO) working group.[35]

11.1.1. Definitions

Evaluable for objective response. Only those participants who have measurable disease present at baseline and have received at least one dose of therapy will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. Participants who exhibit objective disease progression or die prior to the end of the first month will also be considered evaluable.

11.1.2. Disease Parameters

Measurable disease. Bidimensionally, contrast-enhancing, measurable lesions with clearly defined margins by CT or MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measurable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

Non-measurable evaluable disease. Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with maximal diameter < 1cm.

11.1.3. Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

11.1.4. Response Criteria

Complete response (CR). All of the following criteria must be met:

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.

b) No new lesions.

c) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.

d) Participants must be on no steroids or on physiologic replacement doses only.

e) Stable or improved non-enhancing (T2/FLAIR) lesions.

f) Stable or improved clinically, for clinical signs and symptoms present at baseline and recorded to be disease related. Participants with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial response (PR). All of the following criteria must be met:

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.

b) No progression of non-measurable disease.

c) No new lesions.

d) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.

e) The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.

f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.

g) Stable or improved, for clinical signs and symptoms present at baseline and recorded to be disease related clinically.

Participants with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Progressive disease (PD). The following criterion must be met:

a) 25% increase in sum of the products of perpendicular diameters of enhancing lesions (over best response or baseline if no decrease) on stable or increasing doses of corticosteroids

*and/or one or more of the of the following:*

b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids steroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).

c) Any new lesion.

d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the investigator, but it is recommended that a decline in the Karnofsky Performance Score (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration, unless attributable to co-morbid events or changes in corticosteroid dose.
e) Failure to return for evaluation due to death or deteriorating condition.

Stable disease (SD). All of the following criteria must be met:
a) Does not qualify for CR, PR, or progression.
b) All measurable and non-measurable sites must be assessed using the same techniques as baseline.
c) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
d) Stable clinically. Unknown response status. Progressive disease has not been documented and one or more measurable or non-measurable lesions have not been assessed.

11.1.5. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6. Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.7. Response Review

Review of MRI or CT scans will be performed by Dr. Wen or his designee.

### 11.2. Seizure Response

Seizure response will be evaluated every 4 weeks for the secondary endpoint of time to seizure recurrence, measured from the date of surgery. Seizure frequency will be monitored using a seizure diary form completed by participants and reviewed every 4 weeks. Baseline seizure frequency will be defined by the number of clinical seizures reported by participants in the month preceding surgery. Seizure freedom is defined by the absence of seizures.

## 12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

### 12.1. Data Reporting

12.1.1. Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2. Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

### 12.2. Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall

PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

### 12.3. Collaborative Agreements Language

N/A

## 13. STATISTICAL CONSIDERATIONS

This is a pilot study with a primary electrophysiologic outcome and a secondary exploratory clinical outcome of seizure response. The protocol is statistically powered to detect a meaningful reduction in peritumoral hyperexcitability as measured by high frequency activity on ECoG. For the secondary outcome, this protocol is intended to estimate the seizure response effect size of early perampanel treatment on tumor-associated seizures in HGG.

### 13.1. Study Design/Endpoints

**Pilot Study: Preliminary Study**

- Primary objective: Compare rates of peritumoral HFOs (mean number of HFOs per minute) between participants treated with perampanel versus standard of care.
- Secondary objective: Compare time to seizure recurrence between participants treated with perampanel versus standard of care up to the time of HGG progression.
- Maximum total accrual: 10 participants in Cohort 1, 10 participants in Cohort 2.
- Sample size justification: Using the mean HFO rate across participants receiving standard of care (Cohort 2) as the normalized ineffective rate ($P_1$=1.0), we define a target effective rate for the treatment arm (Cohort 1) of $P_2$=0.60. Using a two sample power calculation, the intended sample size of 10 participants in each cohort will provide 82.5% power to detect a true 40% or greater reduction in the normalized mean HFO rate with perampanel compared to standard of care ($\alpha$=0.05, two-sided).
- Statistical methods for primary objective: The primary endpoint is the mean number of HFOs per minute. This will be averaged across participants in each cohort, and compared using the Mann-Whitney U test (two-sided, $\alpha$=0.05). In sensitivity analyses, we will compare HFO rates between cohorts stratified by potential confounding variables, including temporal lobe tumor location, IDH1/2 mutation, and pre-operative seizures.
- Statistical methods for secondary objective: The secondary endpoint is the time to first post-operative seizure. Time to first post-operative seizure will be estimated in time-to-event analysis from the date of surgery using the Kaplan-Meier method. Comparison

between Cohort 1 and Cohort 2 will be performed using the log-rank test ($\alpha$=0.05). In sensitivity analyses, we will compare time to first post-operative seizure between cohorts stratified by potential confounding variables, including temporal lobe tumor location, extent of resection (gross total vs subtotal resection), presence of IDH1/2 mutation, and presence of pre-operative seizures.
- Data processing and statistical analysis will be performed using R 3.5.3 (The R Foundation for Statistical Computing).
- These results will be used to support or refute the hypothesis that perampanel has targeted anti-epileptogenic activity in glioma-associated epilepsy, and may inform the design and feasibility of future clinical studies of targeting the glutamatergic pathway in this patient population.

**Correlative Analysis: Intraoperative Stereotactic Molecular Imaging**
- Aim 1: Correlate lactate/pyruvate ratio by mass spectrometry with HFO rate in adjacent ECoG electrodes.
- Aim 2: Correlate glutamate and GABA signal intensities by mass spectrometry imaging with HFO rate in adjacent ECoG electrodes.
- Aim 3: Correlate anti-seizure drug signal intensity by mass spectrometry imaging with HFO rate in adjacent ECoG electrodes.
- Statistical analysis: correlations will be measured using Spearman's rank correlation coefficient.

13.2. Sample Size, Accrual Rate and Study Duration

A total of 20 evaluable participants will be accrued within one year (up to 10 participants per cohort). Up to an additional 12 months of follow-up will be required on the last participant accrued to observe the participant's response to protocol therapy, for a total study duration of 2 years. There are no defined ethnic or racial accrual targets.

### 13.3. Stratification Factors

N/A

### 13.4. Interim Monitoring Plan

All participants will undergo continuous safety monitoring.

### 13.5. Analysis of Primary Endpoints

See Section 13.1

### 13.6. Analysis of Secondary Endpoints

See Section 13.1

### 13.7. Reporting and Exclusions

13.7.1. Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.7.2. Evaluation of the Primary Efficacy Endpoint

All participants in Cohort 1 who receive at least one dose of study treatment and all participants in Cohort 2 will be evaluable for response.

## 14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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## APPENDIX A PERFORMANCE STATUS CRITERIA

| **ECOG Performance Status Scale** | | **Karnofsky Performance Scale** | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## APPENDIX B MULTI-CENTER GUIDELINES

N/A

## APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

### Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

Perampanel interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Perampanel interacts with a certain specific enzyme(s) in your liver.

- The enzyme in question is/are CYP3A4, and perampanel is broken down by this enzyme in order to be cleared from your system.
- Perampanel must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of CYP3A4."
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.

- If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
- If you take herbal medicine regularly: You should not take St. John's wort while you are taking perampanel.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you.

Your study doctor's name is Jong Woo Lee, MD, PhD, and he or she can be contacted at 617-732-7432.

## APPENDIX D BIOASSAY TEMPLATES

N/A