

**Protocol Title: Randomized, Double-Blind, Placebo-Controlled Trial of
Lacosamide for Seizure Prophylaxis in Patients with High-Grade Gliomas**

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BRAIN TUMOR TRIALS COLLABORATIVE (BTTC)

BTTC11-01: Randomized, Double-Blind, Placebo-Controlled Trial of Lacosamide for Seizure Prophylaxis in Patients with High-Grade Gliomas

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**A DISCLAIMER STATEMENT FOR BTTC
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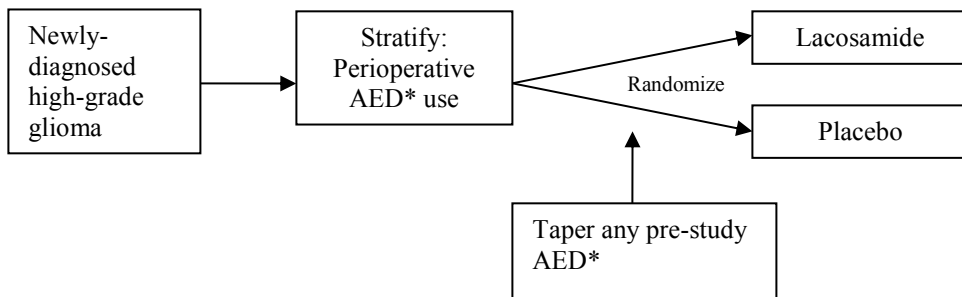
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SCHEMA



*AED (Anti-epileptic drug)

1.0 OBJECTIVES

- 1.1 **Study design:** This is a multicenter, randomized, placebo-controlled trial to assess the efficacy of prophylactic administration of the antiepileptic drug (AED) Lacosamide in patients with newly-diagnosed high-grade glioma (HGG).
- 1.2 **Primary objective:** The primary objective of this study is to determine if prophylactic administration of Lacosamide reduces the risk of seizures in patients with HGG. This will be tested in newly-diagnosed post-operative patients during the first year after tumor diagnosis. The primary endpoint will be time to first seizure.
- 1.3 **Secondary objectives:** The secondary objectives of this study are to determine the one-year risk of first seizure in this patient population and to evaluate patient reported symptoms.
- 1.4 **Exploratory objectives:** The exploratory objectives of this study are:
- To investigate clinical and electroencephalographic predictors of seizures in this patient population.
 - To evaluate the occurrence of symptoms and correlate to seizure activity as well as tolerance to treatment using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) self-reporting tool.

2.0 BACKGROUND

2.1 High-grade gliomas and seizures

High-grade gliomas (HGG) are the most common type of primary brain tumor. There are approximately 22,000 new cases in the United States each year [1]. Seizures are the presenting symptom in approximately 20% of patients with supratentorial HGG and are present at some stage of the illness in 30-50% of patients [2, 3]. The standard of care for HGG patients who present with seizures includes the administration of antiepileptic drugs (AEDs) [4]. Likewise, there is general agreement that AED therapy is not indicated for patients with infratentorial or brainstem tumors due to the extremely low seizure risk. There is, however, no consensus regarding the administration of prophylactic AEDs to patients with supratentorial HGG who have not had seizures. In a 1996 survey of practice patterns according to subspecialty, 33% of radiation oncologists, 50% of oncologists, 53% of neurologists, and 81% of neurosurgeons reported administering prophylactic AEDs. The overall rate of prophylactic AED administration by the 115 physicians in the study was 55% [5]. A 2004 survey of the practice patterns of neurosurgeons in the United States found similar results. Of the 367 respondents, 285 (77.7%) reported the routine use of prophylactic AEDs in patients with HGG [6]. Finally, a retrospective study showed that 27% of 164 brain tumor patients treated in Canada between 2003 and 2005 received phenytoin despite no history of seizures [4].

2.2 Previous studies

A number of small retrospective studies have evaluated the usefulness of AED therapy in glioma patients without a history of seizures and have produced conflicting results:

	Total # of Patients	# of Patients on AEDs	Outcome
Boarini <i>et al.</i> [7]	71	33	Odds ratio for seizure 0.41 (95% CI 0.14-1.19). No patients with therapeutic AED levels had seizures; 18% of untreated patients did.
Moots <i>et al.</i> [8]	36	4	No seizures in AED group compared with 31% in untreated patients ($p=0.60$).
Mahaley and Dudka [9]	59	Unreported	Odds ratio for seizure 1.63 (95% CI 0.52-5.14)

The few prospective studies reported to date have included patients with gliomas, brain metastases and meningiomas. The results of these studies have also been inconclusive.

	Total # of Patients	# of Patients on AEDs	Outcome	Comments
Franceschetti <i>et al.</i> [10]	63	41	Odds ratio for seizure in the AED group 0.36 (95% CI 0.07-1.76).	Only 23/63 patients had gliomas. AEDs included phenytoin and phenobarbital.
Forsyth <i>et al.</i> [11]	100	46	Odds ratio for seizure in the AED group was 0.82 (95% CI 0.33-2.01).	Only 40/100 patients had gliomas. Median follow-up period of 5.4 months. This study had a high non-compliance rate (45% of patients had low AED levels).
Glantz <i>et al.</i> [5]	74	37	Odds ratio for seizure in the AED group was 1.7 (95% CI 0.6-4.6).	This was a prospective, placebo-controlled, randomized study of valproic acid. Only 15/74 patients had gliomas.
North <i>et al.</i> [12]	81	42	Odds ratio for seizure in the AED group was 1.85 (95% CI 0.56-6.12).	This was a prospective, non-placebo-controlled, randomized study of phenytoin. Only 32/81 patients had gliomas.

Many brain tumor patients are treated with AEDs partly because they have had a craniotomy. It is unclear, however, whether prolonged prophylactic AED therapy reduces the frequency of seizures after craniotomy. Foy *et al.* [13] completed a prospective trial involving 276 consecutive supratentorial craniotomy patients (including 50 with meningiomas) who were randomized postoperatively to receive AEDs (carbamazepine or phenytoin) or no treatment. There was no difference in the incidence of seizures (37%) or death between the two groups, suggesting that prophylactic AED therapy may not be routinely necessary after craniotomy. In contrast, a meta-analysis by Kuijlen *et al.* [14] determined that prophylactic AEDs tended to prevent postoperative seizures, but this effect was not statistically significant ($p = 0.1$, one-tailed).

In 2000, the Quality Standards Subcommittee of the American Academy of Neurology (AAN) reviewed the evidence concerning the efficacy of prophylactic AEDs in patients with all brain tumor types [15]. Because the numbers of patients in the studies reviewed were small, they performed a meta-analysis of the four available randomized studies addressing this issue. They concluded that there was no evidence of a significant benefit of prophylactic AEDs and recommended as a practice standard that they not be administered. A shortcoming of their meta-analysis relative to glioma patients, however, is that it included 110 glioma patients and 218 non-glioma tumor patients (145 brain metastases, 46 meningiomas and 17 sellar tumors). Because the majority of patients were those with metastatic tumors, a patient population with a lower incidence of seizures and a shorter life expectancy than patients with HGGs, the efficacy of prophylactic AEDs in HGG patients in particular remains an open question. In accordance with this view are the results of the 2004 survey of 367 neurosurgeons cited above. The AAN practice parameters discouraging the use of prophylactic AEDs remain largely ignored by this physician group [6, 16].

2.3 Side effects of AEDs

AED use is associated with many potential side effects that can have a negative impact on a patient's quality of life. Approximately 20-25% of glioma patients treated with phenytoin and undergoing cranial irradiation develop a morbilliform rash [17], and a small percentage develop Stevens-Johnson syndrome [18]. Stevens Johnson syndrome has also been described in glioma patients receiving carbamazepine [19], and patients receiving phenobarbital have an increased incidence of shoulder-hand syndrome [20]. Additional side effects of AEDs include cognitive impairment, myelosuppression, and liver dysfunction, all of which appear to be more common in brain tumor patients than other patient groups. Overall, 23.8% of brain tumor patients on AED therapy experience side effects severe enough to warrant a change or discontinuation of AED therapy [15]. Although carefully controlled studies are lacking, newer AEDs such as levetiracetam, pregabalin, and lacosamide appear to have more favorable adverse effect profiles [4].

AEDs also have clinically significant interactions with other drugs commonly used in brain tumor patients. Phenytoin induces hepatic metabolism and significantly reduces the half-life and bioavailability of dexamethasone [21, 22]. Conversely dexamethasone may also reduce phenytoin levels [23]. A number of chemotherapeutic agents commonly used in brain tumor patients, such as carmustine (BCNU), interact with phenytoin, causing lower levels, and potentially breakthrough seizures [24]. In addition, many AEDs, including phenytoin and carbamazepine, stimulate the cytochrome P450 enzyme system, markedly accelerating the metabolism of many chemotherapeutic agents, including nitrosoureas, procarbazine, paclitaxel, 9-aminocamptothecin, thiotepa, topotecan, irinotecan, cyclophosphamide, and methotrexate [15, 25-30]. As a result, the optimal doses of these chemotherapeutic agents in patients taking enzyme-inducing AEDs are frequently much higher and less predictable than in patients not on AEDs.

2.4 Seizures and symptoms

Seizures may result in injuries or life-threatening complications such as status epilepticus or aspiration pneumonia. More often, however, seizures restrict patients' independence; in most states, driving is prohibited for 6-12 months after a seizure. Patients whose jobs involve driving or working in dangerous circumstances (e.g., painters, electricians) become unable to work and suffer financial consequences. Patients also experience debilitating anxiety about whether or when a

seizure may occur. In brain tumor patients, seizures can be associated with worsening of other neurologic symptoms, such as weakness or cognitive symptoms [31]. Direct injury to the patient, as well as secondary injuries to others, can occur with seizure activity [5]. AEDs can also be associated with side effects and symptoms, including fatigue, drowsiness, and cognitive effects such as decreased memory and difficulty concentrating. These symptoms may interfere with activity and mood and impair quality of life.

2.5 Lacosamide

Lacosamide (Vimpat®) is an oral AED that was FDA-approved in 2008 as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.

A pharmacokinetic-pharmacodynamic (efficacy) analysis was performed based on the pooled data from the 3 efficacy trials for partial-onset seizures. Lacosamide exposure is correlated with reduction in seizure frequency. However, doses above 400 mg/day do not appear to confer additional benefit in group analyses. Lacosamide is completely absorbed after oral administration with negligible first-pass effect with a high absolute bioavailability of approximately 100%. Food does not affect the rate and extent of absorption. The maximum lacosamide plasma concentrations occur approximately 1 to 4 hours post-dose after oral dosing, and elimination half-life is approximately 13 hours. Steady state plasma concentrations are achieved after 3 days of twice daily repeated administration. Pharmacokinetics of lacosamide is dose proportional (100-800 mg) and time invariant, with low inter- and intra-subject variability. Compared to lacosamide, the major metabolite, O-desmethyl metabolite, has a longer T_{max} (0.5 to 12 hours) and elimination half-life (15-23 hours).

The efficacy of lacosamide as adjunctive therapy in partial-onset seizures was established in three 12-week, randomized, double-blind, placebo-controlled, multicenter trials in adult patients. Patients enrolled had partial-onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant AEDs. During an 8-week baseline period, patients were required to have an average of ≥ 4 partial-onset seizures per 28 days with no seizure-free period exceeding 21 days. In these 3 trials, patients had a mean duration of epilepsy of 24 years and a median baseline seizure frequency ranging from 10 to 17 per 28 days. 84% of patients were taking 2 to 3 concomitant AEDs with or without concurrent vagal nerve stimulation. Study 1 compared doses of lacosamide 200, 400, and 600 mg/day with placebo. Study 2 compared doses of lacosamide 400 and 600 mg/day with placebo. Study 3 compared doses of lacosamide 200 and 400 mg/day with placebo. In all three trials, following an 8-week Baseline Phase to establish baseline seizure frequency prior to randomization, subjects were randomized and titrated to the randomized dose (a 1-step back-titration of lacosamide 100 mg/day or placebo was allowed in the case of intolerable adverse events at the end of the Titration Phase). During the Titration Phase in all 3 trials, treatment was initiated at 100 mg/day (50 mg given twice daily) and increased in weekly increments of 100 mg/day to the target dose. The Titration Phase lasted 6 weeks in Study 1 and Study 2 and 4 weeks in Study 3. In all three trials, the Titration Phase was followed by a Maintenance Phase that lasted 12 weeks, during which patients were to remain on a stable dose of lacosamide. A reduction in 28 day seizure frequency (Baseline to Maintenance Phase) as compared to the placebo group was the primary variable in all three trials. The criteria for statistical significance was $p < 0.05$. A statistically significant effect was observed with lacosamide treatment (Figure 1) at doses of 200 mg/day (Study 3), 400 mg/day (Studies 1, 2, and 3), and 600 mg/day (Studies 1 and 2).

Lacosamide is well-tolerated and has no known drug-drug interactions. In controlled clinical trials, the rate of discontinuation as a result of an adverse event was 8% and 17% in patients randomized to receive lacosamide at the recommended doses of 200 and 400 mg/day, respectively, 29% at 600 mg/day, and 5% in patients randomized to receive placebo. The adverse events most commonly leading to discontinuation were dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and vision blurred. Abnormalities in liver function tests have been observed in controlled trials with lacosamide in adult patients with partial-onset seizures who were taking 1 to 3 concomitant AEDs. Elevations of ALT to $\geq 3 \times$ the upper limit of normal (ULN) occurred in 0.7% (7/935) of lacosamide patients and 0% (0/356) of placebo patients. One case of hepatitis with transaminases $> 20 \times$ ULN was observed in one healthy subject 10 days after lacosamide treatment completion, along

with nephritis (proteinuria and urine casts). Serologic studies were negative for viral hepatitis. Transaminases returned to normal within one month without specific treatment. At the time of this event, bilirubin was normal. The hepatitis/nephritis was interpreted as a delayed hypersensitivity reaction to lacosamide.

A list of possible adverse events is provided in Section 3.12. This includes events reported by patients treated with lacosamide in all clinical trials in patients with partial-onset seizures, including controlled trials and long-term open-label extension trials, as well as events identified during post approval use of lacosamide. Because the latter are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most frequently reported adverse events include dizziness, vertigo, diplopia, blurred vision, nystagmus nausea/vomiting, diarrhea, fatigue, headache, somnolence, tremor, ataxia, and imbalance. Post approval adverse events of potential significance include bradycardia and rash.

Lacosamide is associated with additional rare but potentially serious adverse effects. Lacosamide may increase the risk of suicidal thoughts or behavior. The drug causes dose-dependent PR prolongation and should therefore be used with caution in patients with known conduction problems, or with severe cardiac disease such as myocardial ischemia or heart failure. Lacosamide administration may predispose to atrial arrhythmias (atrial fibrillation or flutter), especially in patients with diabetic neuropathy and/or cardiovascular disease. Syncope and multi-organ hypersensitivity have been reported.

2.6 Summary and rationale

There is no consensus among neurologists, neurosurgeons, and oncologists regarding the need for prophylactic AEDs among newly-diagnosed and peri-operative HGG patients who have not experienced seizures. Unfortunately, data regarding prophylactic AED use is scant and inconclusive. Most of the available evidence comes from older, small studies that enrolled patients with brain metastases and benign tumors in addition to gliomas. Furthermore, these studies universally evaluated prophylaxis with first-generation AEDs such as phenytoin, phenobarbital, carbamazepine, and valproic acid. These drugs have high rates of adverse effects compared to newer AEDs, and they have important interactions with other drugs including corticosteroids and chemotherapeutics. Recently developed AEDs such as lacosamide are effective, safe, and well-tolerated. Lacosamide has no known drug interactions and does not require serum level monitoring. Despite limited published data, in many neuro-oncology centers newer AEDs such as levetiracetam, pregabalin, and lacosamide are emerging as the drugs of choice for seizure prophylaxis. A definitive clinical trial is needed to determine whether prophylactic AED therapy may reduce the risk of first seizures in this patient population. In addition, evaluation of the impact of newer generation AEDs is needed to provide support to the use in this patient population.

3.0 DRUG INFORMATION

3.1 **Drug Name:** Lacosamide (Vimpat®)

3.2 **Chemical Name:** (R)-2-acetamido-N-benzyl-3-methoxypropionamide (IUPAC)

3.3 **Molecular Formula:** C₁₃H₁₈N₂O₃

3.4 **Molecular Weight:** 250.30

3.5 **Appearance:** Lacosamide is a white to light yellow powder.

3.6 **How supplied:**

Lacosamide tablets are available in 50, 100, 150, and 200 mg strengths. The study will provide drug adequate for 3 months of treatment at a time.

3.7 **Formulation:**

Lacosamide tablets contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropylcellulose, hypromellose, lecithin, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, and dye pigments as specified below:

Lacosamide tablets are supplied as debossed tablets and contain the following coloring agents:

50 mg tablets: red iron oxide, black iron oxide, FD&C Blue #2/indigo carmine aluminum lake

100 mg tablets: yellow iron oxide

150 mg tablets: yellow iron oxide, red iron oxide, black iron oxide

200 mg tablets: FD&C Blue #2/indigo carmine aluminum lake

3.8 **Storage and Stability:**

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F).

3.9 **Mechanism of Action:**

The precise mechanism by which lacosamide exerts its antiepileptic effects in humans remains to be fully elucidated. *In vitro* electrophysiological studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. Lacosamide binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein which is mainly expressed in the nervous system and is involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown.

3.10 **Pharmacology:**

A pharmacokinetic-pharmacodynamic (efficacy) analysis was performed based on the pooled data from the 3 efficacy trials for partial-onset seizures. Lacosamide exposure is correlated with the reduction in seizure frequency. However, doses above 400 mg/day do not appear to confer additional benefit in group analyses.

Lacosamide produced a small, dose-related increase in mean PR interval. At steady-state, the time of the maximum observed mean PR interval corresponded with T_{max} . The placebo-subtracted maximum increase in PR interval (at T_{max}) was 7.3 ms for the 400 mg/day group and 11.9 ms for the 800 mg/day group. For patients who participated in the controlled trials, the placebo-subtracted mean maximum increase in PR interval for a 400 mg/day VIMPAT dose was 3.1 ms in patients with partial-onset seizures and 9.4 ms for patients with diabetic neuropathy.

Lacosamide is completely absorbed after oral administration. The oral bioavailability of lacosamide tablets is approximately 100%. Food does not affect the rate and extent of absorption.

The volume of distribution is approximately 0.6 L/kg and thus close to the volume of total body water. Lacosamide is less than 15% bound to plasma proteins. It is primarily eliminated from the systemic circulation by renal excretion and biotransformation. After oral and intravenous administration of 100 mg [^{14}C]-lacosamide, approximately 95% of radioactivity administered was recovered

in the urine and less than 0.5% in the feces. The major compounds excreted were unchanged lacosamide (approximately 40% of the dose), its O-desmethyl metabolite (approximately 30%), and a structurally unknown polar fraction (~20%). The plasma exposure of the major human metabolite, O-desmethyl-lacosamide, is approximately 10% of that of lacosamide. This metabolite has no known pharmacological activity. Lacosamide is a CYP2C19 substrate. The relative contribution of other CYP isoforms or non-CYP enzymes in the metabolism of lacosamide is not clear. The elimination half-life of the unchanged drug is approximately 13 hours and is not altered by different doses, multiple dosing or intravenous administration.

3.11 **Pre-clinical Toxicology:**

There was no evidence of drug related carcinogenicity in mice or rats. Mice and rats received lacosamide once daily by oral administration for 104 weeks at doses producing plasma exposures (AUC) up to approximately 1 and 3 times, respectively, the plasma AUC in humans at the maximum recommended human dose (MRHD) of 400 mg/day. Lacosamide was negative in an *in vitro* Ames test and an *in vivo* mouse micronucleus assay. Lacosamide induced a positive response in the *in vitro* mouse lymphoma assay. No adverse effects on male or female fertility or reproduction were observed in rats at doses producing plasma exposures (AUC) up to approximately 2 times the plasma AUC in humans at the MRHD.

3.12 **Human Toxicity:**

Likely (occurring in more than 20% of patients)

- Dizziness

Common (occurring in 3 – 20% of Patients)

- Vertigo
- Diplopia
- Blurred vision
- Nausea
- Vomiting
- Diarrhea
- Fatigue
- Headache
- Ataxia
- Somnolence
- Tremor
- Nystagmus
- Imbalance (possibly with associated falls)

Rare but Serious (occurring in fewer than 3% of patients)

- Suicidal ideation or behavior
- PR prolongation, first degree AV heart block
- Atrial fibrillation or flutter
- Syncope
- Multi-organ hypersensitivity reactions (also known as Drug Reaction with Eosinophilia and Systemic Symptoms, or DRESS)

3.13 Clinical Pharmacokinetic Properties:

The pharmacokinetics of lacosamide has been studied in healthy adult subjects (age range 18 to 87), adults with partial-onset seizures, adults with diabetic neuropathy, and subjects with renal and hepatic impairment. Lacosamide is completely absorbed after oral administration with negligible first-pass effect with a high absolute bioavailability of approximately 100%. The maximum lacosamide plasma concentrations occur approximately 1 to 4 hours post-dose after oral dosing, and elimination half-life is approximately 13 hours. Steady state plasma concentrations are achieved after 3 days of twice daily repeated administration. Pharmacokinetics of lacosamide are dose proportional (100-800 mg) and time invariant, with low inter- and intra-subject variability. Compared to lacosamide, the major metabolite, O-desmethyl metabolite, has a longer T_{max} (0.5 to 12 hours) and elimination half-life (15-23 hours).

3.14 Administration: Oral.

3.15 Supplier:

Lacosamide is commercially available, but study drug and identical placebo will be supplied by UCB.

3.15.1 Agent Distribution:

Ordering Study Agent/s:

See Section 15.3.2

3.16 Agent Storage and Accountability:

The investigator is responsible for the proper and secure physical storage and record keeping of investigational agents received for BTTC protocols. Specifically, the investigator must:

- Maintain a careful record of the receipt, use and final disposition of all investigational agents received, using the NCI Agent Accountability Record Form (DARF), <http://ctep.cancer.gov/forms/index.html>.
- Store the agent in a secure location, accessible to only authorized personnel, preferably in the pharmacy.
- Maintain appropriate storage of the investigational agent to ensure the stability and integrity of the agent.
- Unused, expired or defective study agent should be destroyed by the site's pharmacy in accordance with their drug disposal/destruction policy or standard operating procedure. The destruction of the study agents will be documented in their pharmacy accountability records.

The intent of the agent accountability procedures described in this section is to assist the investigator in making certain that agents received from BTTC are used only for patients entered onto an approved protocol. The record keeping described in this section is required under FDA regulation. Investigators are responsible for the use of investigational agents shipped in their name. Even if a pharmacist or chemotherapy nurse has the actual task of handling these agents upon receipt, the investigator is the responsible individual and has agreed to accept this responsibility by signing the FDA 1572, <http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.doc>.

BTTC Procedures for Agent Accountability and Storage

- Each investigational agent should be stored separately by protocol. If an agent is used for more than one protocol, there should be separate physical storage for each protocol. Remember that agents are provided and accounted for on a protocol-by-protocol basis.
- Each agent should be accounted for separately by protocol. If an agent is used for more than one protocol, there should be a separate Drug Accountability Record Form (DARF) for each protocol, <http://ctep.cancer.gov/forms/index.html>. There should be a separate DARF for each agent in a multi-agent protocol.
- Separate accountability forms should be maintained for each different strength or dosage form of a particular agent (e.g., an agent with a 1-mg vial and a 5-mg vial would require a different DARF for the 1-mg vial than for the 5-mg vial).
- The DARF is also designed to accommodate both dispensing records and other agent transaction documentation (e.g., receipt of agent, returns, broken vials, etc.). A copy of the DARF may be found at <http://ctep.cancer.gov/forms/index.html>.
- Unauthorized inter-institutional transfer of BTTC investigational agents from one **participating** institution to another is not permitted. For some protocols the **lead** institution may enter into contractual agreements to forward agents to participating institutions (see BTTC Operations Manual section 2.1).

Verification of Compliance

Investigators are reminded that compliance with procedures to ensure proper agent usage will be reviewed during site visits conducted under the monitoring program. Specifically, site visitors will check that the agent accountability system is being maintained, and will spot-check the agent accountability records by comparing them with the patients' medical records to verify that the agents were administered to a patient entered in the recorded protocol

3.17 Disposition of unused and/or defective Agent:

Investigators/Designees should make every effort to minimize the amount of agent ordered (and returned unused if applicable), (e.g. limit inventories to an 8 week supply or less).

Unused, expired or defective study agent should be destroyed by the site's pharmacy in accordance with their drug disposal/destruction policy or standard operating procedure. The destruction of the study agents will be documented in the DARF.

3.18 Handling of study medication:

The study agent is stored at room temperature. It is required that the site pharmacy follow their standard operating procedures related to the management of Scheduled V substances.

4.0 ELIGIBILITY CRITERIA

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Males and females will be recruited with no preference to gender. No exclusion to this study will be based on race. Minorities will actively be recruited to participate.

Unless otherwise specified in the Inclusion Criteria, all patients must meet the General Eligibility Criteria described below.

All patients who meet the following eligibility criteria must be registered with the Brain Tumor Trials Collaborative via the Office of Multicenter Clinical Research (MDACC OMCR) at the University of Texas, MD Anderson Cancer Center (UT MDACC) prior to starting treatment. The OMCR's registration procedures are described in the Multicenter Procedures section of this protocol. **Patients must initiate study treatment within 14 days after registration.**

General Inclusion Criteria

- 4.1 Patients with histologically confirmed supratentorial high-grade glioma will be eligible for this protocol.
- 4.2 All patients must sign an informed consent indicating that they are aware of the investigational nature of this study.
- 4.3 Patients must have signed an authorization for the release of their protected health information.
- 4.4 Patients must be ≥ 18 years old.
- 4.5 Patients must have a Karnofsky performance status of ≥ 60 .
- 4.6 Women of childbearing potential must have a negative β -HCG pregnancy test documented within 2 weeks prior to registration.
- 4.7 In the opinion of the treating investigator, patients must have adequate cognitive abilities to complete the neurocognitive components of the study.
- 4.8 Patients must be able to safely swallow pills.
- 4.9 Patients must agree to practice adequate contraception.
- 4.10 Patients must be registered on study within 16 weeks after the surgical procedure that established the diagnosis of High Grade Glioma.

General Exclusion Criteria

- 4.11 Patients must not have any significant medical or psychiatric illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy.
- 4.12 Patients must not have serious intercurrent medical illness. Serious, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 12 months.
 - Transmural myocardial infarction within the last 6 months.
 - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration.
 - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration.
 - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
 - Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
 - Active connective tissue disorders, such as lupus or scleroderma, which in the opinion of the treating physician, may put the patient at high risk for radiation toxicity.
- 4.13 Patients must not be pregnant or breast feeding Patients must not be pregnant because lacosamide produced developmental toxicity in rats following administration during pregnancy. There is insufficient information to determine if lacosamide is safe during lactation.
- 4.14 Patients must not have any disease that will obscure toxicity or dangerously alter, Drug metabolism
- 4.15 Patients must not have a history of heart block or cardiac arrhythmia, including asymptomatic arrhythmias and atrial fibrillation/flutter.
- 4.16 Patients must not have a prolonged PR interval (defined as > 200 ms).
- 4.17 Perioperative anticonvulsants should be tapered as indicated in section [6.2.1.4](#)
- 4.18 Patients must not have a history of any type of seizure for at least 10 years prior to registration.

5.0 STRATIFICATION/DESCRIPTIVE FACTORS

For the purposes of statistical analysis, patients will be stratified based on use or non-use of peri-operative AEDs and by institution

6.0 TREATMENT PLAN

6.1 General

All patients who meet eligibility criteria must be registered with the Brain Tumor Trials Collaborative Office of Multicenter Clinical Research (MD Anderson OMCR) at the University of Texas, MD Anderson Cancer Center (UT MD Anderson). Patients must initiate study treatment within 14 days after registration. All patients will be monitored for clinical evidence of toxicity as described in section 8.0.

6.1.1 Anti-tumor Treatment

Standard and experimental anti-tumor therapies are permitted.

6.1.2 Supportive Care

- a. Dexamethasone should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and discontinued if possible. Prednisone is not permitted because it induces CYP2C19.
- b. Febrile neutropenia may be managed according to the local institution's Infectious Disease guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed.
- c. The use of antiemetics will be left to the investigators' discretion.

d. Other Concomitant Medications

Therapies considered necessary for the wellbeing of the patient may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. No other anti-convulsant medication are allowed while on the study. All concomitant medications must be recorded.

f. Surgery

If neurosurgical management is required for any reason, the procedure must be documented, including the indications for surgery, the surgical operative note and pathology report.

6.1.3 Definition of dose limiting toxicities (DLT):

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If multiple toxicities are seen, the presence of DLT should be based on the most severe toxicity experienced. DLT will be defined as any grade 3 toxicity that:

- Is not amenable to maximal medical management, and
- Is attributable to the study drug, and
- Occurs during treatment with lacosamide or placebo.

6.2 Treatment Plan

6.2.1 All Patients

6.2.1.1 Evaluations During Treatment

The evaluations required for all patients include medical history, physical and neurologic examinations, electroencephalograms (EEGs; optional), electrocardiogram (EKG; at screening only), MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT), Karnofsky Performance Status (KPS), and laboratory tests (at screening only). The schedule of evaluations is provided in Sections 7 and 8.

6.2.1.2 Agent Administration

Lacosamide and placebo will be taken by mouth twice a day, at approximately the same times each day, spaced as close to 12 hours apart as possible. Medication may be taken with or without food. Missed doses should be taken so long as the dose will be taken within 6 hours of the scheduled time. Vomited doses will not be retaken unless the pill can be clearly identified in the vomitus. Patients will be given drug diaries every 3 months to monitor compliance (see Appendix 17.5).

6.2.1.3 Registration/Randomization:

See Section 15.3.2 for registration/randomization procedures.

6.2.1.4 Drug Dose/s and Treatment Schedule:

Patients may be taking peri-operative AEDs at the time of registration. These agents should be tapered off (on the investigator's preferred schedule) over 1-2 weeks. Lacosamide or placebo will be initiated at the same time that the taper commences. The starting dose of lacosamide or placebo will be 50 mg PO bid. Over 4 weeks, the dose should be increased to a target dose of 200 mg bid. A recommended scheme for dose escalation is to increase by 100 mg/day weekly until 200 mg bid is achieved. Deviations from this scheme that achieve a dose of 200 mg bid by 4 weeks will not be considered protocol violations.

6.3 Dose Modifications:

Patients who experience a treatment-related DLT as defined in Section 6.1.3 should have clinical evaluations and/or laboratory testing at appropriate intervals until the toxicity has resolved.

If a patient experiences DLT, the dose may be reduced or the treatment suspended, at the discretion of the treating investigator. Continuing therapy at a reduced dose should be seriously considered because of the risk of seizure associated with sudden cessation of any AED.

Doses between 50 mg bid and 200 mg bid are permissible during the study, and adjustments may be made as deemed appropriate by the investigator. However, every effort should be made to maintain the target dose of 200 mg bid whenever possible.

If a patient experiences DLT at a dose of 50 mg bid, the treatment should be discontinued.

Doses that are reduced for lacosamide or placebo-related toxicity may be re-escalated to the original dose level, if in the opinion of the treating investigator, it is safe to do so.

Treatment may be held for up to 4 weeks, at the investigator's discretion. If the toxicity does not resolve to a level at which the investigator feels comfortable resuming study drug within 4 weeks, or if a patient experiences DLT at a dose of 50 mg bid, the treatment should be permanently discontinued.

For treatment or dose modification related questions, please contact the Study Chair or the MDACC OMCR at UT MDACC at (713) 792-8519 or OMCR_BTTC@mdanderson.org.

7.0 PRETREATMENT EVALUATION

General Requirements

Unless otherwise noted, all pretreatment evaluations must be performed within 14 days prior to the registration. A model study calendar is presented in Figure 8-1.

- 7.1 A complete history and neurological examination (to include demographic information, vital signs, and documentation of the Karnofsky Performance Status per Appendix 17.2) shall be performed on all patients.
- 7.2 Prestudy laboratory tests shall include CBC, differential, platelets, sodium, potassium, bicarbonate, chloride, BUN, serum creatinine, glucose, bilirubin, SGOT, SGPT, alkaline phosphatase, and serum pregnancy test for women of childbearing potential. Patients must agree to practice adequate contraception. The treating physician should use their own discretion regarding how long patient should continue contraception use after discontinuing treatment.
- 7.3 Documentation of tumor diagnosis.
- 7.4 Patients will complete a baseline MDASI-BT (Appendix 17.3) prior to the first dose of study medication at the doctor's office or clinic. At this time the MDASI-BT will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver nurse may read the questions to the patient or assist with marking the severity number or score as described by the patient.
- 7.5 EKG. Required to evaluate PR interval for eligibility.
- 7.6 EEG (optional but should be obtained whenever possible).

8.0 EVALUATION DURING STUDY

General Requirements

Unless otherwise noted, all evaluations may be performed within 14 days before the scheduled date. A model study calendar is presented in Figure 8-1.

- 8.1 Laboratory tests will be obtained only as deemed necessary by the investigator during study treatment.
- 8.2 All relevant information regarding drugs, doses, laboratory examinations, and treatment-related toxicities shall be documented in the patient's medical record and flow sheets.
- 8.3 A complete history and neurologic exam (to include vital signs and documentation of the patient's Karnofsky Performance Status) will be performed at least every 3 months, +/-2 weeks.
- 8.4 Every 4 weeks when the patient is not seen by the study team, telephone contact between the patient and a study clinician (nurse or MD) is required to assess for possible seizure in the preceding month.. The Site to complete the BTTC 11-01 Interim Telephone Contact Checklistform . Calls or visits must occur on the scheduled date or within 2 weeks prior to the scheduled date.
- 8.5 *EEG should be obtained whenever possible to confirm the clinical impression of seizure.* Because the diagnosis of seizure is frequently made by history, this test is optional.
- 8.6 All patients will be followed for overall survival at least every 3 months, when possible. The follow up will continue until 5 years after the End of Study visit. The follow up can take place via telephone contact by the nurse, study coordinator, or MD.
- 8.7 The MDASI-BT (Appendix 17.3) will be administered every 4 weeks in clinic or by telephone *ONLY* by the nurse or MD.
- 8.8 All patients will be evaluated for adverse events at the monthly telephone calls or visits. In addition all serious adverse events will be reported to the OMCR and the study chair as directed in section 15.7.

Figure 8-1. Model Study Calendar.

	Screening	Start of treatment Visit 1^c (Day 1 of Month 1)	On-treatment period Visits 2-4^c (Day 1 of Months 4, 7, 10)	Last treatment visit Visit 5^c (Day 1 of Month 13)
Demographic data	X			
Drug dispensing/return		X	X	X
Re-Order Drug			X^e	
MDASI-BT ^a		X	X	X
Karnofsky Performance Status	X	X	X	X
EKG ^b	X			
Lab tests ^b	X	X		
EEG ^d	X			
Medical and seizure history	X	X	X	X
Physical and neurologic examination	X	X	X	X
Randomization		X		
Recording of adverse events ^a			X	X
Verification of inclusion/ exclusion criteria	X			
Vital signs	X	X	X	X
Written informed consent	X			
Long Term Follow Up	Phone call for survival data every 3 months for 5 years from initial diagnosis date			

- ^a Every 4 weeks by telephone call while on treatment.
- ^b At baseline and then only as clinically indicated (CBC, differential, platelets, sodium, potassium, bicarbonate, chloride, BUN, serum creatinine, glucose, bilirubin, SGOT, SGPT, alkaline phosphatase, serum pregnancy test for women of childbearing potential, and AED levels if appropriate).
- ^c All required evaluations may be performed within 14 days before the scheduled date, except where otherwise noted.
- ^d EEG should be obtained at baseline and to confirm the clinical impression of seizure. Because the diagnosis of seizure is frequently made by history, this test is optional (at both timepoints).
- ^e Reorder drug after phone contact on months 2, 5 and, 8 between visits provided the patient has not experienced a seizure.

9.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

9.1 Definition of Seizure

Patients and caregivers will be educated about signs and symptoms of seizures using a standard education sheet (Appendix 17.5). They will be instructed to contact the investigator immediately for possible seizure activity. For study purposes, confirmed seizures will include any of the following:

1. Simple partial seizures:
 - a) with motor symptoms: focal motor movements, versive/postural movements
 - b) with sensory symptoms: olfactory sensations
 - c) with autonomic signs
 - d) with psychic symptoms (sudden reversible loss of expressive/receptive speech)
2. Complex partial seizures
 - a) with impairment of consciousness only
 - b) with impairment of consciousness plus automatisms (lip smacking, fumbling, etc)
3. Partial seizures with secondarily generalized seizures
 - a) Unconsciousness with myoclonic jerks with or without tongue-bite or stiffening
 - b) Unconsciousness with tonic spasm, without myoclonic jerks, with or without tongue-bite
 - c) Unconsciousness with tongue-bite without myoclonic jerks or stiffening
 - d) Unconsciousness or staring with one of the following preceding symptoms perceived by the patient:
 - A rising feeling from the abdomen to the throat
 - Smelling of odd scents
 - Stiffening or convulsions in the face or limb(s)
 - Turning the head to one side

Excluded attacks are those deemed by the treating physician to be non-neurologic in origin and are comprised of:

- Merely staring
- Exclusively unconscious with or without incontinence for urine
- Solely disturbances of seeing, feeling, or thinking

9.2 Clinical Event Committee

Medical records from the first post-event physician visit and other relevant medical record information will be forwarded to a blinded “clinical event committee” (CEC) that will review source documents and classify events as seizures or otherwise. The study investigators and the CEC will be instructed to utilize a standard seizure definition (Section 9.1). The committee will be composed of board-certified neurologists who have no other involvement with the study. Each event will be adjudicated by 2 independent reviewers. If the reviewers do not agree about the nature of the event, a third

independent reviewer will adjudicate the event. Additional details regarding the clinical event committee are presented in the Clinical Event Committee Charter.

9.3 Patient Reported Outcomes

This study seeks to establish whether the use of the AED lacosamide reduces the occurrence of seizures. However, given the potential side effects and symptoms associated with both seizures and the use of AEDs, it will be important to determine whether if any determined benefit is associated with improvements in symptoms and the interference of symptoms with daily life or does a worsening of these parameters offset the benefit.

Precedence for measuring “non-therapeutic” endpoints exists in oncology research. For example, gemcitabine was approved by the FDA partially as a consequence of the decrease in pain reported in pancreatic patients who were treated, not on the basis of survival improvement which was modest, at best [32]. There have been efforts in neuro-oncology to evaluate secondary endpoints using validated instruments as additional indicators of benefit.

The M.D. Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) allows the self-reporting of symptom severity and interference with daily activities. The MDASI-BT has demonstrated reliability and validity in the adult primary brain tumor patient population [33]. This tool represents a modification of the widely used and validated MDASI, with particular attention to symptoms common in patients with brain tumors. The availability of validated instruments provides an opportunity to prospectively assess the impact of treatment, both positive and negative, on patients. This evaluation of symptom burden in this study will assist in finding the best possible treatment with the least toxicity.

9.3.1 Patient Related Outcome Objectives

1. To evaluate longitudinal changes in symptom measures and determine the impact of the use of AEDs on these parameters.
2. To measure symptom burden over the course of the study period (one year) evaluate differences between patients individual symptom severity, overall mean symptom severity, and difference in scores on the interference items between those on placebo versus those on lacosamide.
3. To describe the variability of symptom severity longitudinally over the follow-up period.

9.3.2 Patient Related Outcome Methods

9.3.2.1 Patient Related Outcome Instruments:

The MDASI-BT will be utilized for this portion of the study. Full instruments are provided in the appendix. In addition, information regarding demographics and treatment history will be collected as part of the larger study and used in this analysis.

The MDASI-BT consists of 23 symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being “not present” and 10 being “as bad as you can imagine.” Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument include those commonly associated with cancer therapies, those associated with increased intracranial pressure, and those related to focal deficits. The questionnaires also include ratings of how much symptoms interfered with different aspects of a patient’s life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of

life. The interference items are also measured on 0 - 10 scales. The average time to complete these instruments is 5 minutes. The MDASI-BT has been translated into 18 languages [33, 34].

9.3.2.2 Patient Related Outcome Data collection:

After enrollment on the clinical trial, patients will complete as baseline measures the MDASI-BT. The patient will continue to complete the MDASI-BT at the time of clinical and seizure evaluation as long as the patient remains on the study, unless clinical deterioration makes self-report not possible before that time. The time when patients are unable to complete the self-report questionnaires will be used as part of the study analysis. The MDASI-BT will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient. A patient caregiver may complete the questionnaires as a patient-preference proxy if the patient's deficits preclude self-report. These reports will be used for descriptive purposes only. For the telephone interview, the research assistant will read the questions to the patient and mark the response indicated by the patient. If the patient rates any symptom as 7 or higher, the research assistant will instruct the patient to alert his or her physician team and the research assistant will also notify the clinical team that the symptom has been rated as severe by the patient. The forms will be reviewed by the principal investigator or research assistant for completion.

9.4 Electroencephalography (EEG)

EEGs will be reviewed in blinded fashion by Jong Woo Lee, MD, PhD, a neurologist with fellowship training in clinical neurophysiology. He will evaluate background organization, presence of interictal epileptiform discharges (e.g., sharp waves, spikes), activity on the ictal/interictal continuum (e.g., periodic lateralized epileptiform discharges), subclinical seizures, and focal slow waves, particularly polymorphic delta waves.

10.0 CRITERIA FOR REMOVAL FROM TREATMENT

10.1 Criteria for Removal from Protocol Treatment:

- a. Completion of one year of therapy.
- b. Unacceptable toxicity (**see Section 6.1.3**).
- c. Seizure (as defined in Section 9.1).
- d. The patient may voluntarily withdraw from treatment at any time for any reason.
- e. Medical or psychiatric illness which in the investigator's judgment renders the patient incapable of further therapy.
- f. Pregnancy.

All reasons for discontinuation of treatment must be documented in the flow sheets.

11.0 STATISTICAL CONSIDERATIONS

11.1 Overview

The primary analysis for this study is a randomized, two-arm, parallel group, multicenter trial enrolling post-operative patients with newly-diagnosed high-grade glioma (HGG). Patients will be randomly assigned to either lacosamide (L) or placebo (P). Patients will be randomized to either treatment using a 1:1 randomization scheme. Based on a retrospective review of available data we assume a 20% seizure risk in the P group and 8% in the L group (after 1 year of observation). Based on these assumptions and assuming that time to first seizure follows an exponential distribution we estimate the hazard ratio between the L and P arms to be 0.374. Additional assumptions of the trial are that patients will be administratively censored after 1 year of follow-up and that 15% of patients will be lost to follow-up. The reason for the first assumption is that risk of seizure is greatest during the first year and as such clinical interest focuses on this time period. Because standard software packages do not incorporate administrative censoring we developed a SAS IML program to estimate the power associated with this clinical trial design.

Based on this simulation program, the maximum fixed sample size to be accrued is 298 patients. The power for this analysis is 83.6% (power based on 1000 simulations). Because we plan 1 interim analysis using an O'Brien-Fleming stopping rule, we will need to adjust the sample size upward using the group sequential-to-fixed sample size ratio of 1.008 [35]. While this ratio is exact for trials with 80% power, it is a conservative lower bound for trials with greater than 80% power [35]. This ratio results in a trial with 302 patients (i.e., the largest even integer greater than 298×1.008). This results in a trial with 151 patients randomized to L and 151 patients randomized to P. The primary measure of efficacy is time to first seizure (TFS). The primary test of the difference in TFS between the treatment arms will be based on the likelihood ratio statistic for the treatment effect in a stratified proportional hazards regression model with anticonvulsant use as the stratification factor. The MDACC DSMB will periodically meet (either once every 6 months or annually) to evaluate safety and efficacy. The interim analysis will take place after 21 events have been observed. We will assess efficacy using an O'Brien-Fleming stopping rule with a nominal critical value of 2.7959 at the interim analysis. A futility analysis based on a conditional power assessment may be performed if the hazard ratio between the two treatment arms is approximately 1. If a conditional power assessment is performed and the conditional power is less than 0.10 the trial will be stopped for futility. The decision to perform this futility analysis will include an assessment of the number of events observed (i.e., at least 50% of the expected 42 events have occurred and all patients have not yet enrolled in the trial). If the study continues to full accrual, the final analysis will take place when all of the patients have either been followed for 1 year or have experienced a seizure event. We will test the null hypothesis $HR=1.00$ against $HR \neq 1.00$ at the 0.05 level. The conditional power for the time-to-event outcome will be computed based on the method described in Design and Analysis of Clinical Trials with Time-to-Event Endpoints (Peace 2009, page 60) and Lan Simon and Halperin (1982).

Descriptive and inferential statistics will be used to summarize the treatment effects. The mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum will be reported for continuous variables by treatment group. For discrete (qualitative) outcomes, descriptive analyses will be based on the distribution of these discrete outcomes and will be reported as percentages and patient counts by treatment. Time to event endpoints will be descriptively summarized by Kaplan-Meier curves. Point and interval estimates of treatment effects will be based on maximum likelihood methods. For binomially distributed variables, we will report proportions, their 95% confidence intervals, differences in proportions and 95%

confidence intervals for the difference in proportions. Estimates of treatment effects for time to event endpoints will be based on the ratio of hazard functions (L: P) using Wald type scores from a Cox proportional hazards regression model. Unless stated otherwise, all statistical tests will be assessed using a two-sided $\alpha = 0.05$ significance level and confidence intervals will be constructed using two-sided 95% and will be based on the normal approximation. Although multiple secondary endpoints will be evaluated we will make no adjustment for multiplicities associated with these multiple tests.

11.2 Method of Analysis

11.2.1 Analysis Population

Intent-to-Treat (ITT) Population

This analysis set will include all subjects who (1) have received at least one dose of study medication; and (2) have no major protocol eligibility violations. Subjects with major eligibility violations that are identifiable based on pre-study entry characteristics will be excluded. Subjects who receive study medication other than that intended will be analyzed according to the therapy they intended to receive. No data collected on or after the first dosing date will be excluded.

Per-Protocol (PP) Population

All evaluable patients who do not experience any major protocol deviation will be included in the per-protocol dataset. This analysis set will include all subjects who (1) have received at least one dose of study medication; (2) have not committed any major protocol violation, and (3) are evaluable for primary endpoint. Subjects who received a treatment regimen other than that intended will be analyzed according to the therapy they received. Data collected after 30 days post permanent discontinuation of the study treatment will be excluded.

Safety Population

The analysis set will include all subjects who have received at least one dose of study medication. Subjects who receive study medication other than that intended will be analyzed according to the study medication received. All data collected up to 30 days after the subject permanently discontinues the study drug will be included in the analysis of this analysis set.

11.2.2 Baseline Characteristics

Demographic and baseline characteristics collected at screening or enrollment will be descriptively summarized on ITT and PP populations using:

- Frequency distributions (n, %) for qualitative outcomes,
- Standard statistical summaries for quantitative outcomes (n, mean, standard deviation, median, 25th percentile, 75th percentile, min, max).
- Both frequency distributions and standard statistical summaries will be reported for ordinal outcomes.

11.2.3 Safety Analysis

All safety analysis will be performed on the safety population.

11.2.4 Extent of Exposure

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of study regimen, inclusive, regardless of temporary interruptions and dose reduction in study drug administration and summarized. Number of treatment cycles will also be summarized.

Dosing information for individual subjects will be listed and reasons for study drug discontinuations will be summarized.

11.2.5 Adverse Events

Clinical and laboratory adverse events will be coded using the NCI's Common Terminology Criteria for Adverse Events (CTCAEv4.0). The CTCAEv4.0 will be attached to the clinical database.

Summaries of unique adverse events will include

- all treatment emergent adverse events,
- all treatment emergent adverse events by the worst grade,
- all related treatment emergent adverse events,
- all related treatment emergent adverse events by the worst grade,
- all adverse events leading to study drug discontinuation

Treatment emergent adverse events are

- Events with onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of the study medication
- Continuing adverse events diagnosed before the start of treatment and getting worse in grade or relationship to treatment after the start of treatment.

Related adverse events include all those classified by the investigator as definitely, probably, or possibly related to the study drugs. Events for which the investigator did not record relationship to study drug will be considered related to study drug.

Multiple events will be counted once only per patient in each summary. In the presentation, Adverse Event Categories will be sorted in alphabetical order. Within Categories adverse events will be sorted in descending order of total events. For summaries by severity, the most severe event will be selected.

Deaths and serious adverse events

Serious adverse events and deaths will be listed. Data from the adverse event page that specify the event is serious will be used to generate the listing.

Summaries of serious unique adverse events will include:

- all serious treatment emergent adverse events,
- all related serious treatment emergent adverse events by the worst grade,

11.3 Patient Reported Outcomes.

The sample size for this trial was based on the primary endpoint of the study.

Received MDASI-BT forms will be checked versus the timing schedule and considered as valid if they fall within 14 days of the scheduled assessment. Compliance rates will be calculated as the number of received valid forms over the number of expected forms. Differences between groups in compliance will be tested by use of Fisher's exact test at every time point. We will use descriptive statistics to describe how patients rate symptom severity and interference with function at each time point. Error bar graphs for each of the symptoms will be constructed at each time point. The proportion of patients rating their symptoms to be 7 or greater (on a 0-10 scale) will also be reported. Differences of at least 2 points will be classified as the minimum clinically meaningful change in the symptom severity and symptom interference measures. For example, an increase of 2 points or more would mean a moderate improvement, whereas a decrease of 2 points or more would be interpreted as moderate worsening. For individual symptoms, a rise in a symptom score means deterioration, whereas a reduced score means improvement of the specific symptom.

Our primary analytic strategy involves the use of a random-effects (or latent growth curve) model to evaluate patient individual and overall longitudinal changes in symptom measures, and determine the impact of the use of AEDs on these parameters. The random-effects model approach provides a generalization to the classic linear regression model. It is ideally suited for analysis of repeated measures data in that it allows for more specific estimation of the correlation structure of the residuals, and more efficiently handles unbalanced designs and is very robust to missing data, without excluding participants or imputing values. In the model, we will include measure time, treatment indicator and their interaction as random effects (i.e., random slopes or latent growth curves). Such a model allows us to evaluate both patient individual and overall longitudinal trajectories of the symptom burden, and also determine the heterogeneity among patient's trajectories (i.e., variance of the random effects). Fit statistics, such as Akaike's Information Criterion (AIC) will be used to select appropriate covariance structure of the dataset. We will use a computer program, PROC MIXED (SAS v9.1 SAS Institute Inc, Cary, NC) to estimate and to test the models with continuous dependent measures. For binary symptom measures, we will use SAS PROC GLMIMX, which provides an adaptation to the mixed model approach for categorical data. To further investigate whether the patient population is consisted of several subpopulations characterized by different longitudinal trajectories. We will also conduct a latent class analysis based on the random-effects model. We allow different latent classes (or subpopulations) have different regression coefficients (i.e., different shapes of growth curves). The AIC will be used to determine the number of latent class and the maximum likelihood method will be used to estimate the unknown model parameters.

11.4 EEG

Because EEGs are optional and are intended to provide exploratory information only, no formal statistical analysis is planned. The analysis will depend on the amount and quality of data obtained.

12.0 DISCIPLINE REVIEW

See sections 9.2 and 9.4.

13.0 PHARMACOKINETICS

Not applicable.

14.0 LABORATORY CORRELATES

Not applicable.

15.0 MULTICENTER PROCEDURES

15.1 General Procedures

The BTTC Operations Manual and Data Submission Forms, on file at all BTTC institutions, document the data management and quality assurance programs for this collaboration. BTTC institutions will follow the guidelines as addressed below and throughout this protocol.

15.2 Principal Investigators

The principal investigator(s) will be responsible for the conduct of the study and monitoring its progress. The responsibility for all reports and forms required by BTTC will be that of the principal investigator(s).

15.3 Procedures for Patient Entry

15.3.1 Centralized Patient Registrations

Patients who are candidates for the study will first be evaluated for eligibility by the local investigator. All patients must be registered both locally and centrally with BTTC.

Before an institution may begin participating in a BTTC protocol, they must complete the following steps:

- Submit all required regulatory documents to the MDACC Office of Multicenter Clinical Research (OMCR) as outlined in the BTTC Operations Manual
- Participate in a site initiation visit, webcast, or conference call
- Receive training regarding study specific CRF's and/or databases

After these requirements have been fulfilled, the participating institution will receive by fax, e-mail, or hard copy memo a Site Activation Notification. Once the Site Activation Notification has been received, the participating institution may begin to register patients to the protocol

15.3.2 Patient Registration/Randomization

BTTC patients will be registered with the MD Anderson OMCR by fax & phone at UT MD Anderson. All eligibility requirements will be checked prior to registration. The status of all regulatory documents will be checked prior to registration. No patient will be entered on protocol if they do not satisfy all regulatory document and eligibility requirements. Generic MD Anderson OMCR registration procedures are also described in the BTTC Operations Manual.

Informed Consent/Authorization

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an Institutional Review Board (IRB) approved consent form.

Patient Registration/Randomization Procedures

Participating institutions must register patients via EDMS, phone, and/or fax with the MD ANDERSON Office of Multicenter Clinical Research at:

EDMS: <https://iview.mdanderson.org/>

Fax: (713) 794-1902

Phone: (713) 792-8519

Email: OMCR_BTTC@mdanderson.org

Registration hours are 8:00 a.m. to 5:00 p.m. Central Standard Time, Monday through Friday, except holidays.

Registrations must be completed after the patient has signed the informed consent and has been determined to be eligible by the local investigator.

At the time of registration the following information will be requested by the MDACC Office of Multicenter Clinical Research (OMCR):

- A faxed copy of a completed and signed, protocol specific, Eligibility Checklist form
- One copy of a Pathology report from the patient's most recent surgery or biopsy
- One copy of the signed and dated Informed Consent/Authorization.

The eligibility checklist form should be prepared and signed prior to faxing to the MD Anderson OMCR. The fax should be followed by a phone call to the MD Anderson OMCR to verify receipt. If the patient fails eligibility screening do not proceed to the registration process.

Patient Number for Participating Institutions

Once eligibility has been established during Registration, the patient from the participating institution is assigned a six character MD Anderson OMCR patient ID number and a protocol specific Accession Number. The patient ID number is unique to the patient and, except for SAE reports, must be used

for registrations onto subsequent protocols and written on all data and correspondence for the patient. The SAE reports must use the protocol specific Accession Number.

Verification of Registration/Randomization

For participating institutions, a Registration Verification Letter for patients registered to BTTC protocols will be faxed or emailed to the registering institution within one working day after the registration is received. The OMCR must be notified in advance of patient cases that may require an expedited registration.

Drug/Placebo Supply and Ordering

This protocol will use the DMI Drug Ordering /Randomization database housed at MD Anderson Cancer Center. Initial drug/placebo supply will be ordered by the Office of Multicenter Clinical Research (OMCR) after the pharmacist has submitted a Pharmacy Initiation Worksheet and the site have been activated for patient enrollment. Drug is ordered from Uintavision (UVI), a drug distributor. Once drug has been received the pharmacist must then send an email to the OMCR acknowledging receipt. When the supply is low for that institution, an automatic email is generated by the DMI Drug Ordering /Randomization database. The email is sent to the pharmacist as well as the OMCR. The OMCR will request re-supply from UVI. Again, the pharmacist must send the OMCR an email when drug is received.

When a site has been activated for patient enrollment, the pharmacist(s) receives a unique User Name and Password from the OMCR IT group that allows access to the DMI Drug Ordering/Randomization database. The pharmacist(s) must not share this information. After a patient has been enrolled, the OMCR also randomizes the patient to drug or placebo. This will also assign bottle numbers for that patient. The pharmacist receives an automatic email from the DMI Drug Ordering /Randomization database. The email contains a link to the database which allows the pharmacist to view the bottle numbers. When a patient is returning to clinic and needs a re-supply, the pharmacist notifies the OMCR via email or fax. The OMCR will then access the database and “request” bottle numbers. Again, the pharmacist is sent a link to the database which will allow them to view the bottle numbers assigned.

Contact information for OMCR:
MDACC Office of Multicenter Clinical Research
Attn: BTTC Project
Fax: 713-794-1902.
Email: OMCR_BTTC@mdanderson.org.

Initiation of Therapy

Treatment may not be initiated until the participating institution receives a faxed or emailed copy of the patient’s Registration Verification Letter from the MDACC OMCR.

All Patients that are eligible to receive therapy must initiate treatment within 14 days after the registration.

The MD Anderson OMCR must be notified in writing of any exceptions to this policy.

Eligibility Exceptions

Eligibility Exceptions will not be granted.

15.4 Data Management

All data will be entered remotely into the computerized data management system located at the MD Anderson OMCR at UT MD Anderson. Designated research staff from the registering institution will enter the data via remote electronic data entry. The protocol specific electronic forms are to be used by the participating sites. All investigators will utilize these forms for Baseline, Treatment, Tumor Evaluation, Off Treatment, Survival, and Off-study data.

Confidentiality

All documents, investigative reports, or information relating to the patient are strictly confidential. Any patient specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the MD Anderson OMCR must have the patient’s full name & social security number “blacked out” and the assigned MD Anderson patient ID number and protocol number written in. Patient initials may be included or retained for cross verification of identification.

15.5 Data Monitoring

All submitted data will be monitored by the MD Anderson Protocol Manager specifically assigned to this protocol. Requests for correction of data deficiencies will be sent via mail to the Institutional Coordinator. Any major deficiencies will be corrected by telephone communication. All data will be monitored for completeness. Key parameters such as drug dosages including attenuations and escalations, toxicity documentation and tumor measurements will be analyzed. All data deficiencies will be corrected within two weeks.

The schedule for data & source document submission is outlined as follows.

Data Set / Source Documents	Schedule for Submission
Regulatory Documents (as described in the BTTC Operations Manual)	Prior to Patient Registration
Eligibility Checklist	Prior to Patient Registration
Copy of signed & dated Informed Consent w/ HIPAA Authorization	Prior to Patient Registration
Baseline Data (To include prior disease/treatment history, and baseline clinical evaluation information)	Within 14 days after the registration date
Baseline Source Documents	Within 14 days after the registration date
Baseline MDASI – BT Questionnaire	Within 14 days after the registration date

Treatment Data (To include treatment (reported in weekly increments), con meds, AE, and clinical evaluation information)	Within 14 days after each quarterly visit
Follow Up Data (the patient interim telephone contact)	Within 14 days after each follow up telephone call or clinic visit (includes the source document for patient interim telephone contact checklist form)
Treatment Source Documents (pill diaries, pill counts, physician orders/prescriptions)	Within 28 days after each quarterly visit
Off Treatment Data	Within 10 days after the last date of protocol treatment
Off Treatment Source Documents (if applicable)	Within 10 days after the last date of protocol treatment
Non-Treatment Data (May include Quality of Life questionnaires, EEG report, etc.)	Within 10 days after each scheduled assessment, event, or activity
Off Study Data	Within 10 days after the date the patient is removed from the study
Off Study Source Documents	Within 10 days after the date the patient is removed from the study
Pharmacy Drug Accountability Record Form Source Document	Within 10 days after the date the patient is removed from the study
Serious Adverse Events	Within 10 days after notification of SAE

15.6 Safety Assessments and Toxicity Monitoring

All patients receiving study agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, CNS observations, physical examination findings, and spontaneous reports of adverse events reported to the investigator by patients. All toxicities encountered during the study will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and recorded quarterly or more often. Life-threatening toxicities that are unexpected and assessed to be possibly related to the study agent/s should be reported immediately to the study Coordinator, Institutional Review Board (IRB), and those that are unexpected and assessed to be possibly related to the study agents should also be reported to the FDA.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Baseline Evaluations Adverse Events Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are also recorded on the Adverse Events Case Report Form.

Adverse events will be reported at least quarterly. In addition all serious adverse events will be reported to the study chair, and the MD Anderson OMCR as directed in section 15.7.

The MD Anderson Cancer Center DSMB will provide oversight for this protocol.

A serious adverse event is any adverse drug experience at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a patient who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

Events *not* considered to be serious adverse events are hospitalizations for the purposes of this protocol and include:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event *not* fulfilling any of the definitions of serious given above and *not* resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

The study will utilize the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE version 4.0 can be downloaded from the BTTC home page (<http://BTTC.cancer.gov/reporting/ctc.html>). All appropriate treatment areas should have access to either a hard copy of the CTCAE version 4.0 or the www version.

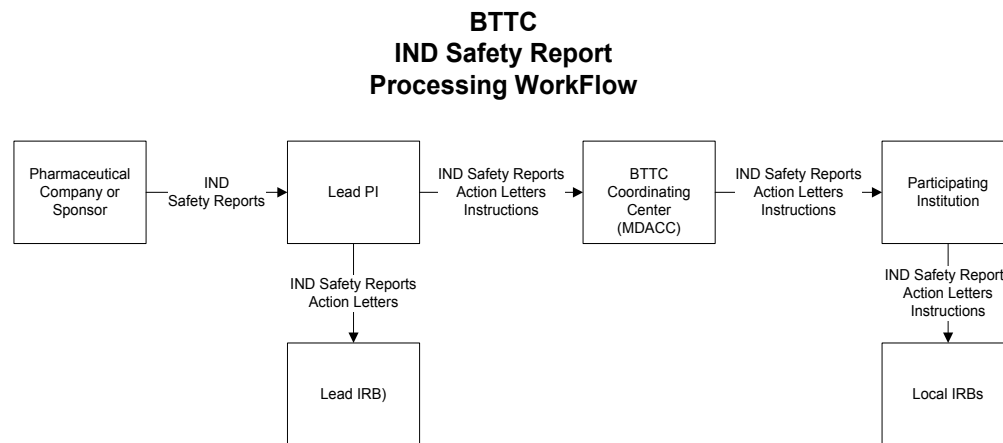
Serious Adverse Events will be reported via the BTTC SAE reporting process. **See section 15.7 for BTTC SAE reporting guidelines.**

Notification of Investigators of Expedited Adverse Events Reported to the FDA

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. In compliance with these FDA regulations, BTTC will notify the BTTC affiliate investigators, via the MDACC Office of Multicenter Clinical Research, by the following methods:

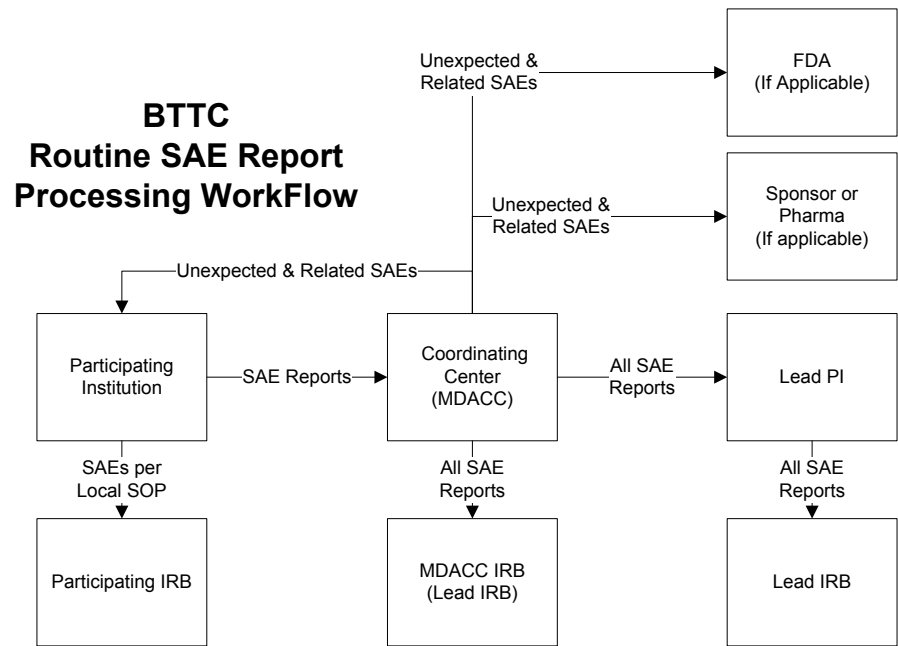
IND Safety Reports –Investigators will be sent a copy of expedited adverse events, which BTTC has sent to the FDA. BTTC will notify consortium investigators via the MDACC Office of Multicenter Clinical Research. Within 7 business days of receipt of the notification the MDACC OMCR will forward the reports to the participating members with protocol specific instructions for IRB submissions, patient notifications, etc. For routine IND Safety Reports BTTC does not generally require an immediate revision to the master protocol and/or model informed consent documents maintained at the MDACC Office of Multicenter Clinical Research. The investigators are to file a copy with their protocol file and send a copy to their IRB according to their local IRB’s policies and procedures.

IND AE Action Letters - These letters are issued by BTTC for those serious adverse events, which warrant an immediate change in the informed consent form and/or protocol. Investigators will be sent a copy of expedited adverse events, which BTTC has sent to the FDA. BTTC will notify consortium investigators via the MDACC Office of Multicenter Clinical Research with the requirement that the model informed consent and or master protocol be amended to include the new event. Immediately upon receipt of the notification the MDACC OMCR will forward the letters to the participating members with protocol specific instructions for IRB submissions, patient notifications, etc. BTTC provides a time frame for which to submit the amendment to the BTTC Protocol and Information Office. The letter from BTTC will specify if accrual to the protocol is to be suspended until the revision is made and whether patients already on study require re-consenting.



15.7 Guidelines for Reporting Serious Adverse Events to BTTC

All patients receiving agents will be evaluated for safety. Local IRB SAE reporting procedures are to be followed by all Institutions. At the same time all SAEs must also be reported to the Lead Principal Investigator and the BTTC Coordinating Center.



BTTC SAE reporting requirements and time frames for reporting to the BTTC Coordinating Center are described below:

Adverse Event Reporting for Investigator-Initiated Clinical Trials			
UNEXPECTED EVENT		EXPECTED EVENT	
Grade 2 & 3	Grades 4 and 5	Grades 1-3	Grades 4 and 5
Attribution of Possible, Probable or Definite	Regardless of Attribution		Regardless of Attribution

<p>Expedited report to MDACC OMCR within 5 working days.</p>	<p>Report by phone to MDACC OMCR Within 24 hrs. Expedited report to follow within 5 Working days.</p>	<p>Adverse Event Expedited Reporting is NOT required.</p>	<p>Expedited report, including Grade 5 Aplasia in leukemia patients, within 5 Working days.</p>
<p>Grade 1 – Adverse Event Expedited Reporting not required.</p>	<p>This includes deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 5 working days.</p>		<p>This includes deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 5 working days. Grade 4 Myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.</p>
<p>For Hospitalization Only – Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for phase of study, expected or unexpected and attribution.</p>			
<p>Expedited reporting may not be appropriate for specific expected AEs for certain later Phase II and Phase III protocols. In those situations the AE that will not have expedited reporting must be specified in the text of the approved protocol.</p>			

The BTTC Coordinating Center will maintain documentation of all Serious Adverse Events from each institution. The BTTC Coordinating Center will notify all investigators of any serious and unexpected adverse experiences that are possibly related to the study agent/s. The investigators are to file a copy with their protocol file and send a copy to their IRB according to their local IRB’s policies and procedures.

All serious adverse events that are unexpected and assessed to be possibly related to the study agents must be reported to the FDA by the lead investigator (or their designee) as a 15-day post-marketing ‘Alert Report’. An unexpected adverse event is one that is not already described in the study agent Investigator Brochure(s). The lead principal investigator (or their designee) also has the obligation to report serious adverse events to their IRB, and UCB. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.

The BTTC Coordinating Center will forward all SAE reports to the lead IRB via the lead investigator, FDA (when applicable), and UCB within 2 business days after sending to the lead PI.

UCB, S.A.	FDA Med Watch 15-day Alert Report
FAX: (919) 767-3175 Telephone: (866) 822-0068 x Option 4 E-mail: ds.us@ucb.com	Phone: 1-800-FDA-1008 Fax: 1-800-FDA-0178 or by mail to MedWatch Center for Biologics Evaluation and Research Food and Drug Administration Suite 200N 1401 Rockville Pike Rockville, MD 20852-1448 FAX: 1-800-FDA-0178 or by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857-9787

SAEs should be recorded on a Multicenter SAE Form (Appendix 17.8). Multicenter SAE forms are to be submitted via EDMS or faxed to:

MDACC Office of Multicenter Clinical Research
Attn: BTTC Project
Fax: 713-794-1902
EDMS: <https://iview.mdanderson.org/>
Phone: (713) 792-8519

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original Multicenter SAE SAE report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original Multicenter SAE form.
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally BTTC may contact the reporter for additional information, clarification, or current status of the subject for whom an adverse event was reported.

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that the study agent/s caused or contributed to an adverse event. The following general guidance may be used.

Yes: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

15.8 Guidelines & Procedures for reporting Violations, Deviations and Unanticipated Problems

Neither the FDA nor the ICH GCP guidelines define the terms “protocol violation” or “protocol deviation.” The definition is often left to the Lead Institution IRB. Accordingly, since MDACC is the Coordinating Center and the Protocol Chair must adhere to those policies set by the MDACC IRB, the definitions for protocol violation and deviation as described by the MDACC IRB will be applied for reporting purposes for all institutions participating in the MDACC Multi-center Project. Definitions, reporting guidelines and procedures for reporting violations, deviations and/or unanticipated problems are described in the BTTC Operations Manual.

Protocol violations/deviations/unanticipated problems occurring at a participating institution will be submitted to that institution’s own IRB. A copy of the participating institution’s IRB violation/deviation/unanticipated problem report will be forwarded to the BTTC Coordinating Center by mail, facsimile, or via email (password protected document) within 7 calendar days after the original submission.

MDACC Office of Multicenter Clinical Research
Attn: BTTC Project
Fax: 713-794-1902
Email: OMCR_BTTC@mdanderson.org

BTTC Coordinating Center: Upon receipt of the violation/deviation/unanticipated problem report from the participating institution, the BTTC Coordinating Center will submit the report to the lead Protocol Chair for review. Subsequently, the participating institution’s IRB violation/deviation/unanticipated problem report will be submitted to the MD Anderson Cancer Center IRB for review.

15.9 Institutional Review

Each cooperating center will submit the protocol to its own IRB. Documentation of the IRB approval will be forwarded to the MDACC OMCR at UT MDACC before a patient from that institution can be registered on protocol. No changes in the protocol will be allowed unless approved by the principal investigator and BTTC.

15.10 Protocol Revisions and Closure

Non life-threatening revisions: BTTC investigators will receive written notification of protocol revisions regarding non life-threatening events.

Life-threatening revisions: BTTC investigators will receive telephone notification of life-threatening revisions with follow-up by fax and/or e-mail. Life-threatening protocol revisions will be implemented immediately.

Protocol closures and temporary holds: BTTC investigators will receive email notification of protocol closures and holds. Closures and holds will be effective immediately. Centers will be updated on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

15.11 Quality Assurance

The BTTC Quality Assurance procedures and reports are described in detail in the BTTC Operations Manual. However, an abbreviated description is provided below.

BTTC Quality assurance measures are provided by three mechanisms: ongoing in-house monitoring of protocol compliance, on-site audits, and response reviews. All data submitted to the MD Anderson OMCR at UT MD Anderson will be monitored in-house for timeliness of submission, completeness, and adherence to protocol requirements. Data monitoring will begin at the time of patient registration and will continue during protocol performance and completion. The MD Anderson Protocol Manager will perform the ongoing protocol compliance monitoring with the support of the BTTC study investigators.

In the absence of a sponsor monitoring requirement, or agency, institutions participating in BTTC Protocols may be subject to on-site auditing conducted by the MD Anderson OMCR as described in the MD Anderson OMCR's Multi-Center Audit Plan for the BTTC consortium. The Multi-Center Audit Plan does not replace the in-house monitoring described in this manual. On-Site auditing combined with the in-house monitoring are intended to enhance the reliability and validity of clinical trial data from BTTC institutions through the use of routine monitoring & auditing procedures.

15.12. Guidelines and Procedure for Unblinding Treatment

The site/treating Principal Investigator may request unblind the patient's treatment under certain circumstances:

- (1) A life –threatening event;
- (2) protocol-defined seizure activity;
- (3) An AE that is concerning to the site Primary Investigator
- (4) At the time study treatment is discontinued.

The unblinding procedure is outlined below. All parties must strictly adhere to the procedure in order to maintain protocol integrity.

1. The treating physician will call and email Dr. Norden and/or his back up to request the unblinding.
2. The treating physician completes the Unblinding Request form:
3. The treating physician will sign and date the completed request form.
4. The treating physician will scan and e-mail the completed unblinding request form to Dr. Norden or designee and cc MDA Anderson OMCR BTTC Staff (omcr_bttc@mdanderson.org)
5. If Dr Norden, or his back-up, approves the unblinding, he will sign, date, scan, and email the Unblinding Request form to the study statistician, Dr Ying Yuan, Dr. Yuan's back-up, and cc the M.D. Anderson OMCR and the requesting physician.
6. Dr Yuan, and/or his back-up, will unblind the patient, and email **the treatment assignment to the treating physician only**. Dr. Yuan will follow up by sending the completed patient unblinding notification memo to the requesting physician.
7. The treating physician will document the unblinding request and outcome in the patient's chart following their institution's policy and procedures **within 24 hours of the unblinding.**
8. The OMCR will notify the MDA IRB and the MD Anderson DSMB of routine patient unblindings at the time of the annual protocol approval. The OMCR will notify the DSMB of each emergency unblinding as they occur.
9. All research staff involved in the activity for this protocol should continue to remain blinded to drug assignment/randomization.
10. If the unblinded patient experienced an SAE, the SAE is to be processed per the protocol, BTTC Operation's Manual, and the institution's policy and procedure. Patient will be taken off treatment and followed for 30 days after last dose or until the event has been resolved.

Contact Information:

NAME	PHONE NUMBER	EMAIL ADDRESS
- Andrew Norden, M.D. (study chair)	617-632-2166	anorden@partners.org
Mark Gilbert, M/D. (Dr. Norden's back-up)		
Ying Yuan, Ph.D. (study biostatistician)	713-563-4271	yyuan@mdanderson.org
Jean Caputo (1st back up to Dr Yuan)	713-794-4164	jcaputo@mdanderson.org
Tim Newell (2nd back up for Dr. Yuan)	713-792-8391	renewell@mdanderson.org
MD Anderson OMCR Sr. CRS	713-792-8519	OMCR_BTTC@mdanderson.org

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17.0 **APPENDICES**

- 17.1 NCI Common Terminology Criteria for Adverse Events
- 17.2 Karnofsky Performance Status
- 17.3 MD Anderson Symptom Inventory for Brain Tumors (MDASI – BT)
- 17.4 Sample Drug Diary and Pill Count
- 17.5 Patient Education Sheet
- 17.6 Patient Unblinding Request Memo
- 17.7 Patient Unblinding Notification Memo
- 17.8 Multicenter SAE Form

17.1 **NCI Common Terminology Criteria for Adverse Events**

This study will utilize the CTCAE version 4.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE version 4.0 can be downloaded at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

17.2 **Karnofsky Performance Status and Neurological Exam**

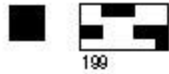
Patient's performance status and Neurologic Exam will be graded according to the following scales:

Karnofsky Performance Status

KPS 100	Normal; no complaints; no evidence of disease
KPS 90	Able to carry on normal activity; minor signs or symptoms of disease
KPS 80	Normal activity with effort; some sign or symptoms of disease
KPS 70	Cares for self; unable to carry on normal activity or do active work
KPS 60	Requires occasional assistance, but is able to care for most personal needs
KPS 50	Requires considerable assistance and frequent medical care
KPS 40	Disabled; requires special care and assistance
KPS 30	Severely disabled; hospitalization is indicated, although death no imminent
KPS 20	Very sick; hospitalization necessary; active support treatment is necessary
KPS 10	Moribund; fatal processes progressing rapidly
KPS 0	Dead

17.3 MD Anderson Symptom Inventory for Brain Tumors (MDASI-BT)

(The MDASI – BT is created by the OMCR programming staff upon request for each protocol. The standard MDASI – BT questionnaire is used as a template. This form will contain coding “landmarks” that enable the data to be scanned into the MDACC data repository for MDASI results. Please contact the OMCR to obtain the questionnaire that is to be attached to the protocol.)



Date: / /
(month) (day) (Year)

Participant's Initials:

PLEASE USE A BLACK INK PEN BTTC 11-01 Patient #:

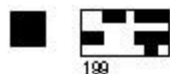
MDASI BT
Protocol Number: BTTC11-01
PI: Andrew Norden MD, MPH
Protocol Acc #:

MD. Anderson Symptom Inventory (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present	As Bad As You can Imagine									
	0	1	2	3	4	5	6	7	8	9	10
1. Your pain at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Your fatigue (tiredness) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Your nausea at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Your disturbed sleep at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Your feeling of being distressed (upset) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Your shortness of breath at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Your problem with remembering things at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Your problem with lack of appetite at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Your feeling drowsy (sleepy) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Your having a dry mouth at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. Your feeling sad at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. Your vomiting at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13. Your numbness or tingling at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14. Your weakness on one side of the body at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15. Your difficulty understanding at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16. Your difficulty speaking (finding the words) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>



Date: / /
(month) (Day) (Year)

Participant's Initials:

BTTC11-01 Patient #

PLEASE USE A BLACK INK PEN

MDASI BT
Protocol Number: BTTC11-01
PI: Andrew Norden MD, MPH
Protocol Acc #:

	As Bad As You can Imagine										
	0	1	2	3	4	5	6	7	8	9	10
17. Your seizures at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18. Your difficulty concentrating at its WORST	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19. Your vision at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20. Your change in appearance at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
21. Your change in bowel pattern (diarrhea or constipation) at its WORST	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
22. Your irritability at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Interfered Completely										
	0	1	2	3	4	5	6	7	8	9	10
23. General activity?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
24. Mood ?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
25. Work (including work around the house) ?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
26. Relations with other people?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
27. Walking?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
28. Enjoyment of life ?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>



Date: / /
(month) (Day) (Year)

MDASI BT

Protocol Number: BTTC11-01

Participant's Initials:

PI: Andrew Norden MD, MPH

BTT C11-01 Patient #:

Protocol Acc #:

PLEASE USE A
BLACK INK PEN

MD. Anderson Symptom Inventory (MDASI - BT)

Participant
Signature

Date

Clinician
Signature

Date

17.4 Pill Diary Patient Initial: _____ BTTC ID #: _____ Bottle #: _____ Month #: _____

This calendar is for you to indicate that you took the drug(s) according to the instructions. Please put a check mark after each dose.

Please sign this calendar at the end of the cycle and bring the calendar and all study drug bottle(s) back to your next clinic visit.

DOSES: Lacosamide/Placebo _____ mg by mouth twice a day as close to 12 hours apart as possible.

Day 1 _____ _____ mg a.m. _____ p.m. _____	Day 2 _____ _____ mg a.m. _____ p.m. _____	Day 3 _____ _____ mg a.m. _____ p.m. _____	Day 4 _____ _____ mg a.m. _____ p.m. _____	Day 5 _____ _____ mg a.m. _____ p.m. _____	Day 6 _____ _____ mg a.m. _____ p.m. _____	Day 7 _____ _____ mg a.m. _____ p.m. _____	
Day 8 _____ _____ mg a.m. _____ p.m. _____	Day 9 _____ _____ mg a.m. _____ p.m. _____	Day 10 _____ _____ mg a.m. _____ p.m. _____	Day 11 _____ _____ mg a.m. _____ p.m. _____	Day 12 _____ _____ mg a.m. _____ p.m. _____	Day 13 _____ _____ mg a.m. _____ p.m. _____	Day 14 _____ _____ mg a.m. _____ p.m. _____	
Day 15 _____ _____ mg a.m. _____ p.m. _____	Day 16 _____ _____ mg a.m. _____ p.m. _____	Day 17 _____ _____ mg a.m. _____ p.m. _____	Day 18 _____ _____ mg a.m. _____ p.m. _____	Day 19 _____ _____ mg a.m. _____ p.m. _____	Day 20 _____ _____ mg a.m. _____ p.m. _____	Day 21 _____ _____ mg a.m. _____ p.m. _____	
Day 22 _____ _____ mg a.m. _____ p.m. _____	Day 23 _____ _____ mg a.m. _____ p.m. _____	Day 24 _____ _____ mg a.m. _____ p.m. _____	Day 25 _____ _____ mg a.m. _____ p.m. _____	Day 26 _____ _____ mg a.m. _____ p.m. _____	Day 27 _____ _____ mg a.m. _____ p.m. _____	Day 28 _____ _____ mg a.m. _____ p.m. _____	
		Patient Signature: _____				Date: _____	

PILL COUNT DOCUMENTATION:

TO BE COMPLETED BY CLINICAL RESEARCH STAFF

PATIENT INITIAL: _____ **BTTC I.D. #** _____ **Bottle #** _____ **MONTH #** _____

DOSE OF LACOSAMIDE PRESCRIBED: _____ **MG, PO**

LACOSAMIDE tablets are available in 50, 100, mg strengths. The study will provide drug adequate for 3 months of treatment.

XX

DATE DISPENSED: _____ (mm/dd/yy) **QUANTITY OF BOTTLES DISPENSED:** _____

QUANTITY OF 50 MG TABLETS DISPENSED: _____

QUANTITY OF 100 MG TABLETS DISPENSED: _____

NUMBER OF _____ **MG TABLETS PER DAY REQUIRED TO ACHIEVE PRESCRIBED DOSE:** _____

XX

*******DO NOT RETURN UNUSED TABLETS TO THE PATIENT*******

RETURN PILL/BOTTLE COUNT DATE: _____ (mm/dd/yy)

Has the patient taken the dose scheduled for this date? YES NO

QUANTITY OF BOTTLES RETURNED: _____

QUANTITY OF 50 MG TABLETS RETURNED: _____ **QUANTITY OF 100 MG TABLETS RETURNED:** _____

17.5 Patient Education Sheet Seizure Information Sheet

You are part of a study looking at prevention of seizures with lacosamide (Vimpat). It is important that you understand what a seizure is, what to do if one occurs, and what to report to the health care team.

What is a seizure?

The brain is the control center of the body. Cells in the brain send electrical signals out to other parts of the body to make them work together with the brain. Brain cells work like little switches to turn off and on the signals that control movement, sensation, and consciousness. When someone has a seizure, it's as if some of the cells get stuck in the "on" position and cause signals that make parts of the body shake. A person having a seizure may lose awareness of surroundings, have uncontrollable, jerky movements, or experience visual changes.

Are all seizures the same?

No. There are two major kinds of seizures:

Partial seizures happen when only one side of the brain is affected, usually the side where the tumor is located. It then affects one side of the body, opposite the side of the tumor. There are two general types of partial seizures, simple and complex partial.

- **Simple partial seizures:** the person will stay awake and can usually respond to you. They may experience any of the following based on the location of the tumor:
 - Jerking or twitching of the arm, leg or face
 - Numbness or tingling of the arm, leg or face
 - Blinking lights or objects on one side of their vision
- **Complex partial seizures:** most commonly occur with tumors in the temporal lobe. The person is awake, but may not be able to respond. They may also experience any of the following:
 - Brief staring spells, like in a trance
 - Unable to speak or have garbled speech
 - Lip smacking, chewing
 - Experience a déjà vu sensation
 - Doing repetitive motions

Generalized seizures happen when the whole brain is suddenly swamped with electrical signals. The person will have loss of consciousness. The person may experience a simple partial seizure or complex partial seizure that then becomes a generalized seizure, or they may experience only a generalized seizure. They may also experience any of the following symptoms:

- Arms and legs stiffen. Then they may begin jerking
- Loss of control of urine or bowels
- Biting of the tongue or sides of the mouth
- Decreased breathing

What are the stages of a seizure?

Seizures often occur suddenly and are unexpected. Some common stages are:

- **Preictal:** Sometimes the person will experience a period of time before the seizure (minutes to days in length), in which they feel differently. This is called a preictal period. Not everyone has a preictal period. Some common symptoms are:
 - An aura in which the person tastes, smells or hears something that is not there
 - Sense of déjà vu
 - Unusual sensation in the stomach or nausea

17.5 Patient Education Sheet Seizure Information Sheet

You are part of a study looking at prevention of seizures with lacosamide (Vimpat). It is important that you understand what a seizure is, what to do if one occurs, and what to report to the health care team.

What is a seizure?

The brain is the control center of the body. Cells in the brain send electrical signals out to other parts of the body to make them work together with the brain. Brain cells work like little switches to turn off and on the signals that control movement, sensation, and consciousness. When someone has a seizure, it's as if some of the cells get stuck in the "on" position and cause signals that make parts of the body shake. A person having a seizure may lose awareness of surroundings, have uncontrollable, jerky movements, or experience visual changes.

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- **Simple partial seizures:** the person will stay awake and can usually respond to you. They may experience any of the following based on the location of the tumor:
 - Jerking or twitching of the arm, leg or face
 - Numbness or tingling of the arm, leg or face
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- **Complex partial seizures:** most commonly occur with tumors in the temporal lobe. The person is awake, but may not be able to respond. They may also experience any of the following:
 - Brief staring spells, like in a trance
 - Unable to speak or have garbled speech
 - Lip smacking, chewing
 - Experience a déjà vu sensation
 - Doing repetitive motions

Generalized seizures happen when the whole brain is suddenly swamped with electrical signals. The person will have loss of consciousness. The person may experience a simple partial seizure or complex partial seizure that then becomes a generalized seizure, or they may experience only a generalized seizure. They may also experience any of the following symptoms:

- Arms and legs stiffen. Then they may begin jerking
- Loss of control of urine or bowels
- Biting of the tongue or sides of the mouth
- Decreased breathing

What are the stages of a seizure?

Seizures often occur suddenly and are unexpected. Some common stages are:

- **Preictal:** Sometimes the person will experience a period of time before the seizure (minutes to days in length), in which they feel differently. This is called a preictal period. Not everyone has a preictal period. Some common symptoms are:

- An aura in which the person tastes, smells or hears something that is not there
- Sense of déjà vu
- Unusual sensation in the stomach or nausea
- **Ictal:** This is the time when a seizure is occurring. Typically lasts seconds to minutes
- **Postictal:** After the seizure has occurred, the person may have time when they still cannot respond or may need to sleep. With a complex partial or generalized seizure, the person may not remember what has happened during the ictal phase.

Can a seizure cause injury to the brain or body?

The average seizure does not have any lasting effects on the brain. However, it can be a warning sign and can cause damage if it is uncontrolled. If you have a seizure, you need to let your doctor know about it. A seizure is seldom a cause of injury, but there is greater danger if it occurs while swimming, driving, or near a place where a fall could cause an injury.

What is first aid for a seizure?

For a **focal seizure**, watch the person carefully and guide them away from anything that may be harmful.

- Remain calm and stay with the person until the seizure has passed.
- Keep track of time and what symptoms the person has and part of the body involved.

If the person loses consciousness during a focal seizure or has a generalized seizure:

- Try to help them gently to the floor.
- Turn the person on his or her side if they begin to choke or vomit.
- Place something soft under the head to protect it.
- Loosen any tight clothing.
- Do not try to hold the person down to stop the shaking. The movements will stop on their own.

After the seizure is over

- Let the person rest; stay with them and reassure them.
- Try to write some notes about the seizure to share with the doctor. Describe how long the seizure lasted, the area or areas of the body that were shaking, and whether or not there was loss of consciousness or loss of bladder control.

When to call 911

Most seizures do not last long. However get immediate medical help if:

- The seizure is generalized and lasts for more than 5 minutes
- The person does not wake up after the seizure is over.
- Another seizure occurs shortly after the first one.

What special instructions should the seizure patient follow?

- Many state laws keep you from driving for up to 12 months after you have had a seizure. Check with your local authorities and your local physician about when you can begin driving again.
- If medications have been prescribed for seizures, take them exactly as ordered by your doctor.
 - Try to take them around the same time(s) each day.
 - Do not stop taking the medications without first talking to your doctor.
 - Report any unusual side effects to your doctor.
 - Always check with your doctor before taking any other type of medicine.
- Report any signs of infection, such as a sore throat or a fever of 101°F (38.3°C) or higher.

- Practice moderation. Try to spread your daily activities out throughout the day. Don't try to do everything at once.
- Try to avoid extremes of physical or mental stress.
- Avoid alcoholic drinks. An occasional drink may be permitted, but be sure to check with your doctor.
- Study your feelings and your surroundings after a seizure to see if something might have triggered it or if you may have had some warning that it was coming.