

Clinical Protocol

A Randomized Open Label Phase II Trial of Aprepitant (Emend) in Combination with Ondansetron Compared to Standard 5HT3 Serotonin Antagonist (Ondansetron) in the Prevention of Acute and Delayed Chemotherapy Induced Nausea and Vomiting (CINV) in Glioma Patients receiving a Temozolomide Based Regimen

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1 INTRODUCTION

1.1 Chemotherapy-Induced Nausea and Vomiting (CINV)

While the incidence of CINV has been significantly reduced since the advent of dexamethasone and first generation selective serotonin subtype 3 (5HT₃) receptor antagonists (RA), nausea and emesis continue to rank among the most distressing side effects of chemotherapy and are reported in up to 50% and 76% of chemotherapy-treated patients respectively. CINV can be classified into phases which include; 1) acute CINV (A-CINV), occurring within the 24 hours post treatment; 2) delayed (D-CINV), occurring after 24 hours and up to 120 hours or 2 days after a multi-dose regimen. Although all first generation 5HT₃ - RA demonstrate efficacy in preventing A-CINV, effective prevention of D-CINV has not been achieved. Even with strict adherence to ASCO/NCCN antiemetic evidence based guidelines, D-CINV occurs in 50% of patients. While physicians and nurses are fairly accurate in predicting A-CINV, they dramatically underestimate rates of D-CINV. Poorly controlled CINV can also lead to numerous medical conditions such as dehydration, electrolyte imbalance, and Mallory-Weiss tears resulting in re-hospitalization (increased medical costs), reduced efficacy and impairment of psychological, social, emotional as well as physical well-being; all which may affect QOL. Thus, challenges remain in the prevention of CINV, which include assessing the efficacy substance P/neurokinin 1(NK1) receptor antagonist.

1.2 Aprepitant

There are three selective first generation 5-HT₃-RA (serotonin-3) available for the prevention of acute CINV including **ondansetron**, dolasetron, and granisetron. Although these agents have some pharmacological differences in 5-HT₃ receptor binding affinity, selectivity and metabolism, these minor variations have not resulted in clinically meaningful differences in efficacy among them. According to current evidence-based and NCCN guidelines, these 5-HT₃-RA are equivalent with regard to efficacy and are therapeutically interchangeable when used at equipotent doses. All first-generation 5-HT₃-RA demonstrate considerable efficacy in preventing acute CINV with acute response rates as single agents ranging from 50% to 70%.

Emend (Aprepitant) is a substance P/neurokinin 1(NK1) receptor antagonist. It has little or no affinity for 5-HT₃, corticosteroid or dopamine receptor, the targets of existing antiemetic therapies for CINV, but has selective high affinity of human substance P neurokinin 1 (NK1). It is usually given as a one-time dose of 125 mg pre-chemotherapy followed by a 2 day 80 mg regimen to control CINV. Aprepitant undergoes extensive liver metabolism that primarily involves the CYP3A4 gene with minor involvement of the CYP1A2 and CYP2C19 genes. Enzyme inducing anticonvulsant drugs (EIAED) and other chemotherapy agents such as temozolomide may be affected by the use of this antiemetic agent.

1.2.1 Chemical properties of aprepitant

Aprepitant is a substance P/neurokinin 1 (NK₁) receptor antagonist and is the first and only member of this new therapeutic class of antiemetic medications.

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK₁) receptors. Aprepitant has little or no affinity for serotonin (5-HT₃), dopamine, and

corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting.

Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK₁ receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT₃ receptor antagonist, ondansetron, and the corticosteroid, dexamethasone, and inhibits both the acute and delayed phases of cisplatin-induced emesis.

A computerized search of the published medical literature identified references that described the pharmacology and mechanism of action of aprepitant. These references are summarized below.

1.2.2 Aprepitant mechanism of action

Aprepitant has a novel antiemetic mechanism of action as a brain penetrant, competitive reversible and selective high-affinity antagonist at human substance P/NK₁ receptors. Preclinical studies involving PET imaging of the healthy human brain have demonstrated that substance P/NK₁ receptors are located centrally in the brain stem. Substance P has been shown in animals to cross the blood-brain barrier. Tattersall and colleagues demonstrated that central nervous system penetration of an NK₁ receptor antagonist was required for antiemetic activity. The NK₁ receptor antagonists are required to penetrate and enter into the CNS to exert their antiemetic effect at the centrally located NK₁ receptors. Tattersall and colleagues also demonstrated that a nonbrain penetrant NK₁ receptor antagonist was ineffective.

1.2.3 Aprepitant in chemotherapy induced nausea and vomiting

Cisplatin is one of the most emetogenic cancer chemotherapeutic agents administered in clinical practice. The vomiting induced by cisplatin follows a biphasic pattern. During the first phase, the peak frequency of vomiting occurs in 6 to 8 hours post-chemotherapy and diminishes in approximately 12 hours. During the second phase, vomiting begins at approximately 16 hours post-chemotherapy and peaks between 24 and 72 hours.

Hesketh P.J. et al. (2003) conducted a post hoc analysis of the two Phase IIa CINV clinical studies of aprepitant, to compare the time course of the anti-emetic effect of the NK₁ receptor antagonist, aprepitant, a 5HT₃ antagonist or the combination of both drugs. It is important to note that the dose and the dosing regimen in the Phase IIa CINV clinical studies were not the final aprepitant regimen that was used in the Phase III CINV clinical studies. In the first study, over the entire period of 7 days post-cisplatin therapy, 31% of patients treated with aprepitant had no emetic episodes compared to 21.7% of patients treated with ondansetron. However, in the first 8 hours post-cisplatin treatment, 82.6% of patients treated with ondansetron had no emesis compared to 36.7% of patients treated with aprepitant. No emesis rates in the ondansetron group declined to 69.6% and 52.2% in the 0 to 16 hour and 0 to 24 hour periods post-cisplatin, respectively, whereas the no-emesis rate for aprepitant group remained unchanged during the 8 to 24 hour period. In the second study, 36% of patients in

the aprepitant treatment group had no emesis compared to 23% of patients in the granisetron treatment group over the 0 to 120 hour period post-cisplatin treatment. Dexamethasone was administered to patients in this study. In the 0 to 8 hour period, 92.2% of patients in the granisetron treatment group had no emesis compared to 49.4 in the aprepitant treatment group. During the 0 to 16 hour and the 0 to 24 hour period, the percent of patients with no emetic episodes continued to decline to 81.1% and 56.7% respectively, in the granisetron treatment group, whereas the percent of patients with no emetic episodes remain unchanged in the aprepitant treatment group. When aprepitant was combined with granisetron, only 20% of the patients experienced emesis during the first 24 hours.

The analysis of the studies for the time course of anti-emetic effect concluded that 5HT₃ receptor antagonists have a better control of emesis during the 8 to 12 hours post-cisplatin in the pathogenesis of CINV associated with highly emetogenic chemotherapy since the serotonin-dependent mechanism appears to be predominate, whereas NK₁ receptor antagonists have better emetic control thereafter, as NK₁-dependant mechanism appears to predominate.

In the two highly emetogenic CINV Phase III studies (Study 1 and Study 2), the estimated time to first emesis after initiation of cisplatin treatment was longer with the aprepitant regimen, and the incidence of first emesis was reduced in the aprepitant regimen group (aprepitant 125 MG on Day 1 and 80 mg on Days 2 and 3, ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg PO on Day 1 and 8 mg PO on Days 2 to 4) compared with standard therapy group (ondansetron 32 mg intravenously and dexamethasone 20 mg orally on Day 1 and dexamethasone 8 mg twice daily on Days 2-4) as depicted in the Kaplan-Meier curve. The curves in both Study 1 and Study 2 appear to be similar up to approximately 16 hours after the administration of cisplatin, but the curves then diverge after that time as the statistical significance with the aprepitant regimen becomes evident. (P-Value <0.001 based on a log rank test for Study 1 AND Study 2; nominal p-values not adjusted for multiplicity.)

In a moderately emetogenic chemotherapy study, the time to first emesis after the initiation of moderately emetogenic chemotherapy was longer for patients in the aprepitant regimen compared with a standard therapy regimen (ondansetron 8 mg BID on Days 1 through 3 and dexamethasone 20 mg on Day 1 only), as depicted in the Kaplan-Meier curve. The aprepitant regimen showed superiority versus the standard therapy regimen at approximately 6 hours, and the gap between the two regimens continued to diverge and widen over the 120 hour (5-day) period.

2 BACKGROUND AND RATIONALE:

Primary glioblastoma multiforme (GBM) is the most lethal type of brain tumor with a median survival rate of approximately 15 months. Unfortunately, the median survival rate for GBM patients has not significantly changed despite over 25 years of research involving a variety of agents and delivery systems. In a recently published population-based study the overall survival of patients with newly diagnosed GBM was 42.6% at 6 months, 17.7% at one year and 3.3% at 2 years. The outlook is somewhat better for less common tumors, such as anaplastic astrocytoma with a 38-50% 2 year survival rate. Despite decades of intensive

investigation, the prognosis for most patients with malignant gliomas remains very poor primarily due to the high resistant to current available therapy. The role of adjuvant chemotherapy in glioma treatment has been controversial. A meta-analysis of 12 randomized trials comparing additional adjuvant chemotherapy to radiation demonstrated only a 5 percent increase (from 15 to 20%) in two-year survival rate. Occasional responses (15%) to single or multiple agent chemotherapy are observed in the setting of recurrent tumor, but these responses are generally of short duration, and cures are rare. Thus, the general consensus in 2002 was that the use of chemotherapy following surgery and radiotherapy produced a marginal benefit over that seen with surgery and radiotherapy alone. However, in 2005, Stupp et al. reported the results of a multi-institutional phase III EORTC trial in which patients with primary glioblastoma multiforme were randomized after surgery to receive either radiation alone or radiation with concurrent temozolomide followed by six cycles of adjuvant temozolomide. The two-year survival was significantly higher (26.4%) for patients receiving radiation and adjuvant temozolomide than for patients receiving radiation therapy alone (10.4%). Recently, Stupp reported an updated overall survival of 27.2% (95% CI 22.2-32.5) at 2 years, 16.0% (12.0-20.6) at 3 years, 12.1% (8.5-16.4) at 4 years, and 9.8% (6.4-14.0) at 5 years with single agent temozolomide. When compared to the 12 trial meta-analysis conducted by Stewart et al mean increased survival time is improved but remains poor. To date, standard therapy for glioma patients currently consists of surgical resection followed by temozolomide and concurrent radiotherapy followed by at least 6 cycles of adjuvant temozolomide. One limitation in the use of this effective regimen in adjuvant temozolomide is its high level of chemotherapy induced nausea and vomiting (CINV) which occurs at a rate of 56%. Thus, it is important to ameliorate toxicities, such as chemotherapy induced nausea and vomiting (CINV) to prevent dose reductions and early termination that lead to poorer overall tumor response rates and decreased quality of life.

Glioma CINV: Currently, we use the standard of care first generation antiemetic, oral ondansetron 8 mg p.o. with each oral temozolomide dose. Several phase II studies have been conducted within the Duke Brain Tumor Center that has examined the CINV in the treatment of patients with malignant glioma. In these studies patients were treated with ondansetron and dexamethasone with intravenous chemotherapy with the hope of preventing CINV. These phase II studies demonstrated that 55% of patients experienced CINV (45% CR: patients did not experience CINV) as defined by the NCI (National Cancer Institute) Common Toxicity Criteria (CTC) version 3.0. These studies measured CINV frequency and did not utilize the standard and acceptable efficacy CR endpoint used in multiple phase III pivotal CINV trials (Aapro 2006; Gralla 2003). Thus a pilot and feasibility study to determine the use of "Ondansetron and Palonosetron (PALO) in the prevention of acute and delayed CINV in forty malignant glioma patients receiving irinotecan in combination with bevacizumab" utilizing the standard efficacy CR endpoint was conducted. The pilot study assessed this primary dichotomous outcome defined as the proportion of patients achieving a complete response (CR) for individual days 1-5 after receiving chemotherapy. A patient was deemed a CR if (1) no emesis or retching was reported on that day; and/or (2) no rescue medication for nausea or vomiting/retching was used on that day. Overall we concluded that 65% of PALO patients had CR versus 60% of ondansetron patients. However, these data did not provide evidence that a difference in CR rate existed between the two treatment groups. Due to the small

sample size, there was inadequate power to conclude that the two treatments had equivalent efficacy. Furthermore, a higher proportion of patients in the ondansetron group who received concomitant oral dexamethasone, a known antiemetic, which could have contributed to the overall ondansetron CR rate. It has been demonstrated that adding dexamethasone to an antiemetic regimen improves overall acute efficacy and prevention of CINV by 20%. Thus, dexamethasone is routinely admixed with 5HT3-RA and administered prior to chemotherapy to enhance efficacy. However, most patients in the pivotal PALO phase III randomized controlled, non-inferiority trials did not receive standard of care intravenous (i.v) dexamethasone. The seminal paper published by in the New England Journal of Medicine established the Stupp regimen as the *gold standard* therapy for glioblastoma patients. This trial documented a 20% CINV rate for adjuvant temozolomide (Stupp, 2005, Supplemental table 1) using 5HT3 RAs as the antiemetic of choice. This CINV rate translates into an 80% CR rate. Oral chemotherapy does not require decadron as a standard antiemetic. We believe that the CINV CR rate of 80% can be improved with adding the substance P/neurokinin 1(NK1) receptor antagonist Aprepitant. Thus, it was recommended that a larger Phase II trial be conducted to determine if improved efficacy exists between Aprepitant in combination with Ondansetron vs. ondansetron alone(standard of care) in glioma patients receiving temozolomide.

CINV risk factors: Characteristics of both the patient and chemotherapeutic agent contribute to the risk of developing CINV. Overall, patients who are under 50 years of age, female and who receive prior treatment with chemotherapy are at increased risk. Chemotherapy in glioma can range in emetogenicity, with moderately and high emetogenic agents causing CINV in > 30% and >90%, respectively, of patients treated. The gold standard Stupp regimen (see Appendix 11.4) has documented a 20% CINV rate for adjuvant temozolomide (Stupp, 2005). This fact places temozolomide in the moderate emetic risk category due to the brain pathology (intracranial edema). It has also been noted that aprepitant may alleviate delayed CINV but may interact with EIAEDS (enzyme- inducing anti-epileptic drugs) causing unacceptable toxicity.

EIAED Interactions: Alterations in the activity of cytochrome P450 enzymes can affect the clearance of chemotherapeutic drugs. Aprepitant, a moderate inhibitor and inducer of cytochrome P450 3A4, is now increasingly used for the prevention of chemotherapy induced nausea and vomiting. However, there is little published data on the potential interaction between enzyme inducing antiepileptic drugs (EIAED) and aprepitant. Thus, in this proposed (study we would like to exclude patients receiving EIAED's due to its unknown interaction with Aprepitant).

Safety of Administration: Three recently published articles describe the administration of aprepitant beyond the currently approved 3 days. Albany et al. (2012) performed a randomized, placebo-controlled Phase 3 study of aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with testicular cancer that were on a 5-day cisplatin combination chemotherapy treatment. In this study, patients receiving 2 consecutive identical courses of 5-day cisplatin-based chemotherapy were randomly assigned to either aprepitant at 125 mg on Day 3 and 80 mg on Days 4-7 or to placebo in their first course of

treatment. They then crossed over to the opposite treatment with their second course. The study found significant improvement in complete response of both acute and delayed CINV with aprepitant, which they defined as “no emetic episodes with no use of rescue medication,” in comparison to placebo. The study also found no increase in observed toxicity in comparison to placebo.

Stiff et al. (2012) performed a randomized, placebo-controlled Phase 3 study of aprepitant in combination with ondansetron and dexamethasone in “patients treated with ablative preparative regimens,” i.e. patients preparing for stem cell transplant. Patients were randomized to receive either 1) dexamethasone and ondansetron every day of the preparative regimen plus 1 additional day combined with aprepitant 125 mg on Day 1 of the preparative regimen followed by 80 mg on each remaining day of the regimen plus 3 additional days or 2) dexamethasone and ondansetron on every day of the preparative regimen plus 1 additional day and a placebo for aprepitant. The study found that patients who received aprepitant had significantly higher rates of complete response, i.e. better control of vomiting, compared to the regimen with placebo. Aprepitant was well tolerated in the study, with only heartburn and asthenia occurring more frequently in the aprepitant arm than the placebo arm.

Lastly, Gralla (2012) offers a review of the Albany et al. (2012) study. Gralla concludes that the Albany et al. trial “provides evidence for a new approach for controlling emesis in multiple-day chemotherapy and highlights many unmet needs in the complete control of emesis for all patients on each cycle of chemotherapy.”

In our trial, we are comparing the use of aprepitant in combination with ondansetron with standard administration of ondansetron alone during the first 5 days of every 28-day cycle of oral temozolomide for patients with malignant glioma (125mg on Day 1 followed by 80 mg on Days 2 -5).

3 STUDY OBJECTIVES

3.1 Primary Objective

To assess CINV efficacy of Aprepitant in combination with Ondansetron vs. Ondansetron alone in preventing acute and delayed CINV (Complete Control (CC): days 1-7) in brain tumor patients during adjuvant temozolomide therapy.

3.2 Secondary Objectives

To assess the efficacy of Aprepitant in combination with Ondansetron vs. Ondansetron alone in preventing acute CINV in brain tumor patients during the acute period (first 24 hours) of receiving adjuvant temozolomide therapy.

To assess the efficacy of Aprepitant in combination with Ondansetron vs. Ondansetron alone in preventing delayed CINV (days 2-7).

To assess the safety and tolerability of Aprepitant administered concomitantly with Ondansetron.

3.3 Exploratory Objectives

To assess the time to treatment failure of Ondansetron treatment with and without Aprepitant.

To explore the effects of age, gender, chemotherapy history, and concomitant glucocorticoid on the efficacy of Ondansetron treatment with and without Aprepitant.

To explore the impact of Aprepitant on quality of life and daily function.

3.4 Efficacy

Primary CINV Efficacy Endpoint: Primary efficacy endpoint is the proportion of patients achieving an acute and delayed complete response (CR: proportion of patients with no emetic episode and no rescue medication).

Complete control (CC): Study days 1–7 (acute and delayed CINV) the proportion of patients achieving complete control (CC); defined as no emetic episode, no need for rescue medication during days 1-7; number of emetic episodes daily; time to first emetic episode; as captured by the MAT (MASCC Antiemesis Tool)/Osoba survey (MASCC refers to Multinational Association for Supportive Care in Cancer™). Severity of nausea and other toxicities measured daily by the NCI Common Toxicity Criteria (version 4.0) (see Appendix 11.5). This tool is used in previous Duke University Medical Center Studies to evaluate toxicity and patient perceptions of cancer treatment-related side effects.

Secondary endpoints of the study include:

Complete response (CR): (1) Assessed from the beginning of study day 1, CR is defined for *acute CINV* as no emetic episode and no use of rescue anti-nausea medication during the first 24 h following chemotherapy administration. An emetic episode is defined as one episode of vomiting or a sequence of episodes in very close succession not relieved by a period of relaxation of at least 1 min, any number of unproductive emetic episodes (retches) in any given 5 min period, or an episode of retching lasting <5 min combined with vomiting not relieved by a period of relaxation of at least 1 min; (2) Complete response (CR) on study days 2–7 (*delayed CINV*) is defined as the proportion of patients achieving a CR during the delayed time period. The data will be captured by the validated MAT/Osoba survey.

Operational definitions of other secondary outcome are as follows: (a) CINV CR: Absence of nausea/vomiting defined as no emetic episode or use of rescue medication; (b) CIV CR: Absence of vomiting episode or the use of vomit medication; (c) CIN CR: Absence of the use of medication to help nausea, or due to concern about the possibility of experiencing nausea.

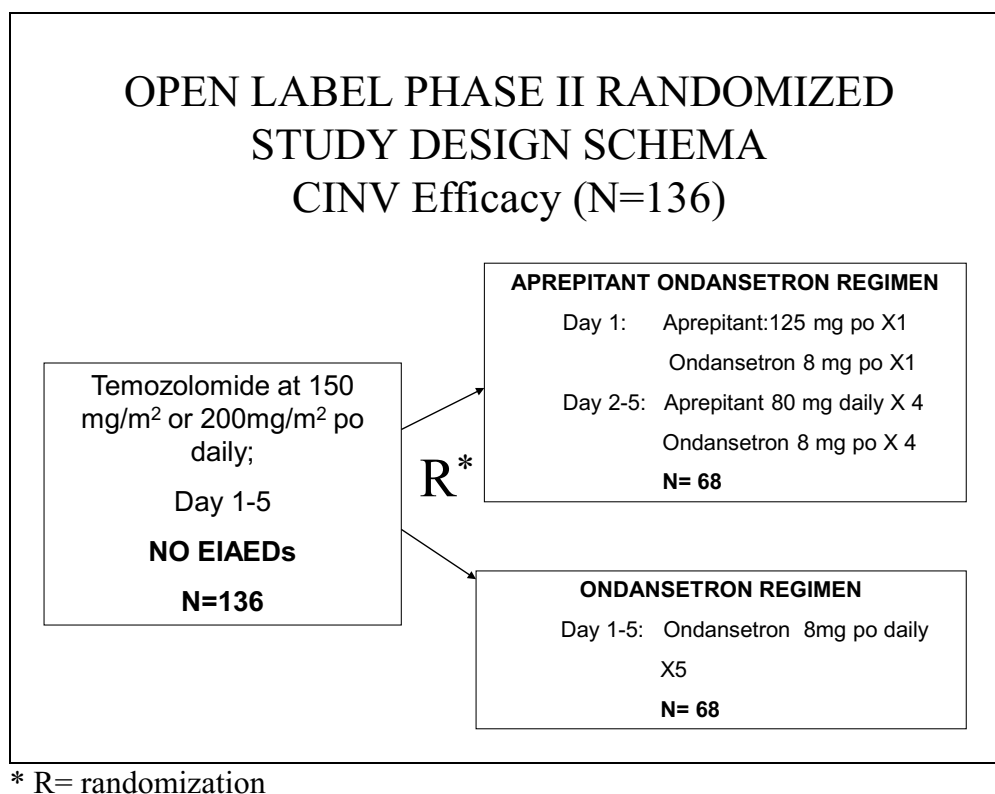
Time to treatment failure (first emetic episode or first need of rescue medication, whichever occurred first): as measured by the MAT/Osoba survey which indicates time of first emetic episode or rescue medication.

Quality of life (QOL): patient's global satisfaction with the antiemetic regimen as measured by the Osoba survey. This survey will be administered at baseline and for day 1 (acute period) and for days 2-7 (delayed period) to determine overall global satisfaction (Acute and delayed combined to determine overall CC, days 1-7).

4 INVESTIGATIONAL PLAN

4.1 Summary of Study Design and Treatment Regimen

One hundred and thirty-six (136) malignant glioma patients receiving temozolomide will be accrued in this open labeled phase II randomized single institution trial of Aprepitant in combination with Ondansetron vs. Ondansetron alone for the prevention of acute and delayed CINV. Sixty-eight (68) patients will be randomized to each arm of the study.



4.2 Aprepitant/Ondansetron:

On day 1, eligible patients will receive a single oral dose of Aprepitant 125 mg p.o, 1 hour before first dose of the 5-day oral temozolomide regimen. This will be followed by Aprepitant 80 mg p.o. on days 2 -5 (1 hour prior to temozolomide). In addition, on days 1-5, eligible patients will receive a single oral dose of Ondansetron, 30 minutes before the first dose of the 5-day oral temozolomide regimen. After the start of chemotherapy, additional rescue antiemetic medication will be at the investigator's discretion.

4.3 Ondansetron:

On days 1-5, eligible patients will receive a single oral dose of Ondansetron, 30 minutes before first dose of the 5-day oral temozolomide regimen. After the start of chemotherapy, additional rescue anti-emetic medication will be at the investigator's discretion.

Patients will be initially screened for eligibility within 14 days prior to study initiation. During this time period, the following will be recorded: physical examination; vital signs and weight; laboratory tests [complete blood count (CBC) with differential, complete metabolic panel (CMP)]; past medical history; concomitant medications; and history of nausea and vomiting. All women of child bearing potential will have pregnancy excluded as standard of care prior to initiation of temozolomide. CINV will be assessed at baseline and for Days 1-7. Follow-up telephone assessment will occur for day 1 and days 2-7, day 15, and 30 (for serious toxicity only) after beginning the study drug(s). All subjects will be followed for a total of 30 days. Patient surveys will be collected to record the following: emetic episodes; use of rescue medication; patient global satisfaction; and severity of nausea, which will be evaluated daily until day 7 via the CINV Patient Survey (MAT/Osoba) (see Section 11.1).

Toxicity will be assessed through adverse event (AE) reporting for a period of 15 days (30 days for serious AEs). After the investigator learns of a serious adverse event (SAE), every attempt will be made to obtain vital sign measurements, laboratory tests at 24 h and 1 week (+/- 2 days) after the SAE (including hematology, blood chemistry, liver function tests and urine analysis), physical examination at 24 h and 1 week (+/- 2 days) after the SAE.

4.4 Pharmacokinetic Sampling

Every attempt will be made to obtain pharmacokinetic (PK) sampling as soon as possible after the investigator learns of a serious adverse event (i.e. NCI CTC Version 4.0, grade 4 non-hematologic toxicity that is probably or definitely related to aprepitant) in relationship to when the study drugs were administered, in order to measure drug (temozolomide and its metabolite, 5-aminoimidazole-4-carboximide (AIC)) concentrations. A PK kit containing collection tubes with stabilizing agent will be sent to the appropriate laboratory drawing and processing the PK blood sample. These samples will be collected and run at the pharmacokinetic lab at Duke University Medical Center (please see Appendix 11.3). Results of the PK sampling would be reported to both the FDA and Merck via adverse event reporting (see section 7). Merck will support the set-up, collection and running of the assay.

4.5 Chemotherapy treatment plan

Glioma patients eligible for the study will receive temozolomide orally according to the standard 5-day schedule every 28 days. The temozolomide will be dosed at either 150 mg or 200 mg per square meter beginning with the first cycle. Patients will receive Aprepitant at 125 mg p.o. on Day 1 and 80mg p.o. qd on days 2 -5 and Ondansetron 8 mg p.o. qd days 1-5 or Ondansetron only 8 mg p.o. qd days 1-5, depending upon the arm of the study to which they have been randomized.

4.6 Study Location

This study will be conducted at The Preston Robert Tisch Brain Tumor Center Clinic at Duke University Medical Center and at the local oncologist's office.

4.7 Study Population

It is expected that 136 patients with gliomas who attend the Preston Robert Tisch Brain Tumor Center Clinic at Duke University Medical Center will be enrolled onto this open-label, randomized, Phase II, 2-Arm Trial in a 12-month period. Approximately 170 patients will be screened for patient eligibility assuming 20% will either not be eligible or not agree to participate in the study. We plan to begin enrollment in the spring of 2013 and enrollment should be completed by summer of 2014.

4.8 Criteria for enrollment

4.8.1 Inclusion criteria

In order to be included in the study, patients must meet all of the following criteria:

1. Patients must have histologically confirmed diagnosis of glioma (either low or high grade) and be either chemotherapy naïve or non-naïve and scheduled to receive temozolomide-based +/- Bevacizumab-based chemotherapy. Patients with recurrent disease whose diagnostic pathology confirmed glioma (either low or high grade) will not need re-biopsy.
2. Age \geq 18 years
3. \leq 2 prior chemotherapeutic regimens
4. Patient is scheduled to receive adjuvant temozolomide at either 150mg/m² or 200mg/m² po X 5 days out of a 28 day cycle +/- Bevacizumab
5. Study participation will occur during the first cycle of the 5 day temozolomide course.
6. An interval of at least 6 weeks between prior surgical **resection** and study enrollment
7. Karnofsky \geq 60%.
8. Hematocrit > 29%, ANC > 1,000 cells/ μ l, platelets > 100,000 cells/ μ l
9. Serum creatinine < 1.5 mg/dl, serum SGOT and bilirubin < 1.5 times upper limit of normal
10. For patients on oral corticosteroids, they must be stable clinically on corticosteroids or tapered off prior to starting the study drug. For patients taking dexamethasone, the dose should not exceed 8 mg qd (or 4 mg BID), if clinically stable, and the dose should not be escalated over entry dose level, if clinically possible. The patient's dose of dexamethasone will be evaluated by the PI, the patient's study physician, and/or the study pharmacist on a case by case basis for safety. All doses of oral corticosteroids will be reduced by 50% to avoid drug to drug interactions with Aprepitant, unless oral corticosteroids are at physiologic dose (e.g. dexamethasone 1mg, prednisone 10 mg, or cortisone 30 mg). It is recommended that oral corticosteroid doses be escalated back to full dose on Day 7 (2 days after Aprepitant is discontinued) based on Aprepitant half-life pharmacokinetic data, and expert clinical opinion.

11. Signed informed consent approved by the Institutional Review Board prior to patient entry
12. If sexually active, patients will take contraceptive measures for the duration of protocol treatment and continue until one month after treatment. The efficacy of hormonal contraceptives during and for 28 days following the last dose of Aprepitant may be reduced. Alternative or back-up methods of contraception must be used.
13. Approved rescue medication for the treatment of nausea and vomiting is permitted at the discretion of the investigator. The rescue antiemetics allowed will include: ondansetron, granisetron and lorazepam.

4.8.2 Exclusion criteria

In order to be included in the study, patients must meet all of the following criteria:

1. Pregnant or breast-feeding (While both aprepitant and ondansetron are classified as Category B drugs, an eligibility criteria for this study is that the patient be scheduled to receive a temozolomide-based chemotherapy regimen +/- bevacizumab, which are Category D and C drugs respectively. Therefore, while not considered necessary for the administration of the current study drugs, a pregnancy test should be a part of normal clinical care for the patients in this study, if the patient is determined to be of child-bearing potential.)
2. No prior nitrosourea (e.g. lomustine, carmustine)
3. Inability or unwillingness to understand or cooperate with study procedures
4. Concurrent administration of CYP3A4 enzyme-inducing anti-epileptic drugs (EIAEDs) including phenytoin, phenobarbital, carbamazepine, oxcarbazepine or primidone (see Appendix 11.2).
5. Prohibited medications:
Patients taking CYP3A4 enzyme inducers and moderate or strong inhibitors will be excluded from this trial. Please refer to the website listed in Appendix 11.2 of the full protocol for updates to this list of medications.
6. Received any drug with potential anti-emetic effect within 24 hours prior to the start of study-designated chemotherapeutic agent: HT3 receptor or substance P/neurokinin 1(NK1) receptor antagonists; Dopamine receptor antagonists (metoclopramide); Phenothiazine anti-emetics (prochlorperazine, thiethylperazine and perphenazine); Diphenhydramine, scopolamine, chlorpheniramine maleate, trimethobenzamide; Haloperidol, droperidol, tetrahydrocannabinol, or nabilone
7. Any vomiting, retching or NCI Common Toxicity Criteria version 4.0 grade 2-4 nausea 24 hours preceding chemotherapy
8. Ongoing vomiting from any organic etiology
9. Will receive radiotherapy of cranium within one week prior to or during the study

4.9 Study Procedures and Study Flow Chart

DAY	-14 to 1	1	2	3	4	5	6 & 7
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SCREENING	X						
MAT Survey	X	X	X	X	X	X	X
Osoba Survey		X	X	X	X	X	X
Toxicity Assessment ^a		Continuous					
Arm 1 Aprepitant in combination with Ondansetron		125 mg PO 8 mg PO	80 mg PO 8 mg PO	80 mg PO 8 mg PO	80 mg PO 8 mg PO	80 mg PO 8 mg PO	
Arm 2 Ondansetron		8 mg PO	8 mg PO	8 mg PO	8 mg PO	8 mg PO	
Temozolomide		X 150mg/m ² or 200mg/m ² PO	X 150mg/m ² or 200mg/m ² PO	X 150mg/m ² or 200mg/m ² PO	X 150mg/m ² or 200mg/m ² PO	X 150mg/m ² or 200mg/m ² PO	

^a If a serious adverse event occurs, toxicity will be assessed for 30 days.

4.9.1 Screening/baseline procedures, study day -14 to study day 1.

Screening procedures may be performed up to the day of chemotherapy just prior to administration of the oral Aprepitant or Ondansetron.

The following procedures are to be completed before admission into the study:

- Signing of the approved informed consent form prior to conducting study required procedures.
- Determination that the patient meets all study inclusion/exclusion criteria.
 - Physical examination, including medical history and neurological examination
 - Vital signs
 - CBC
 - CMP
- MAT survey
- Randomization will be conducted after eligibility criteria are met. The randomization will be overseen by the statistical team designated in key personnel as noted in the BTC SOP (see Appendix 11.6).

4.9.2 Administrative plan and daily procedures

The study team will be collecting data from the tools listed below. Data will be housed in Oracle Clinical (OC). Regular meetings between the study team and primary investigators will occur to review data. The clinical research coordinator (CRC) is required to monitor protocol patients weekly or as many times necessary to obtain toxicities. Toxicities will be obtained via clinical notes or telephone conversations with the local oncology office and /or patient. The National Cancer Institute (NCI) Common Toxicity Criteria (CTC) Version 4.0 will be used to score the adverse events. All graded toxicities will be entered in the OC

database and reviewed together with the Primary Investigator (PI), the data management team, and CRC and confirmed by source documents. Attributions are approved by the primary investigators.

4.9.2.1 Evaluation tools

As stated in “Study design and treatment regimen” the evaluation tools include the following:

- NCI Common Toxicity Criteria (CTC) (version 4.0) (see Section 11.5)
- MAT/Osoba CINV Patient Survey (see Section 11.1)

4.9.3 Subject withdrawal

Patients may be discontinued from the study for any of the following reasons:

- A serious adverse event or a significant change in laboratory value occurs that, in the opinion of the investigator, makes it unsafe for the patient to continue in the study. In this case, the appropriate measures will be taken.
- The patient dies.
- The patient is lost to follow-up. Lost to follow-up in this study identifies a patient with whom no contact of any kind can be established. When a patient is thought to be lost to follow-up, a reasonable effort shall be made to contact the patient.
- The patient requests to be withdrawn from the study.
- The investigator, for any reason, terminates the entire study or terminates the study for that patient or the attending physician requests that the patient be withdrawn for any other medical reason.

5 STUDY MEDICATION

5.1 Aprepitant

5.1.1 Description

Aprepitant is a substance P/neurokinin 1(NK1) receptor antagonist.

5.1.2 Source

Aprepitant is manufactured by Merck Inc.

5.1.3 Dosage and Administration

Subjects will receive a single oral dose of Aprepitant 125 mg p.o, 1 hour before their first dose of the 5-day oral temozolomide regimen. This will be followed by Aprepitant 80 mg p.o.q.d. on days 2 -5, 1 hour before their chemotherapy.

5.1.4 Packaging

No. 3854 — 80 mg capsules: White, opaque, hard gelatin capsule with “461” and “80 mg” printed radially in black ink on the body. They are supplied as follows:

NDC 0006-0461-02 unit-of-use BiPack of 2

NDC 0006-0461-06 unit-dose package of 6.

No. 3855 — 125 mg capsules: Opaque, hard gelatin capsule with white body and pink cap with “462” and “125 mg” printed radially in black ink on the body. They are supplied as follows:

NDC 0006-0462-06 unit-dose package of 6.

5.1.5 Labeling

EMEND (Aprepitant) Capsules

5.1.6 Storage and Handling

Store at 20-25°C (68-77°F) [see USP Controlled Room Temperature].

5.1.7 Disposal

Study drug allocated for the above referenced study, upon completion of the study or upon notice of the drug’s expiration, should be disposed of at the site, pursuant to the Good Clinical Practice (GCP) Guidelines and the Investigator’s Institutional policies. Therefore, unused study drug allocated for the study referenced above should not be returned to Merck.

5.1.8 Drug Ordering

Aprepitant will be provided free of charge by Merck Inc.

5.2 Ondansetron

5.2.1 Description

Ondansetron is a first generation 5-HT₃-RA (serotonin-3).

5.2.2 Source

Ondansetron (Zofran) is commercially available and will not be provided in this study.

5.2.3 Dosage and Administration

Ondansetron will be administered on both arms of the protocol at 8 mg p.o. qd on Days 1- 5 days, 30 minutes prior to each dose of chemotherapy.

5.2.4 Drug Ordering

Ondansetron is commercially available and will not be provided in this study. A prescription for Ondansetron will be given to the patient on both arms of the study.

6 DEFINITION of Adverse Event

6.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product/biologic (at any dose) or device and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example) a symptom or

disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product:

- occurring in the course of the use of a drug, biological product, or device,
- associated with, or observed in conjunction with product overdose, whether accidental or intentional,
- associated with, or observed in conjunction with product abuse, and/or
- associated with, or observed in conjunction with product withdrawal.

An adverse event is also any failure of expected pharmacological or biologic therapeutic action (with the exception of such failure occurring in a clinical trial).

Serious - Any adverse drug, biologic or device experience occurring at any dose that results in any of the following outcomes: death, a life threatening adverse drug experience, requires or prolongs in-patient 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 a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and 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 a home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Non-serious - Any **AE** which does not meet the criteria for a serious adverse event.

Life-threatening - the patient/subject was at immediate risk of death from the **AE** as it occurred.

In addition, the Principal Investigator will have all reports of the following forwarded to him/her:

- Pregnancy (patient or partner) – We acknowledge that these are not serious, unless a serious outcome occurs (e.g. miscarriage, congenital anomaly).
- Overdose – we acknowledge that these are not serious, unless a serious outcome occurs.

Attribution

The Principal Investigator or his designee will document his/her opinion and any supporting laboratory and clinical information of the potential attribution of the study drug to any grade 3 or greater toxicity based on the following guidelines:

Unrelated

This category applies to those toxicities that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)

Unlikely (*must have any two criteria*)

In general, this category can be considered applicable to those toxicities that are judged to be unrelated to the test drug. A toxicity may be considered unlikely if or when:

1. It does not follow a reasonable temporal sequence from administration of the test drug;
2. It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It does not follow a known pattern of response to the test drug;
4. It does not reappear or worsen when the drug is re-administered.

Possible (must have any two criteria)

This category applies to those toxicities for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. A toxicity may be considered possibly related if and when:

1. It follows a reasonable temporal sequence from administration of the test drug;
2. It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It does follow a known pattern of response to the test drug.

Probable (must have any two criteria)

This category applies to those toxicities that are felt with a high degree of certainty to be related to the test drug. A toxicity may be considered probably related if and when:

1. It follows a reasonable temporal sequence from administration of the test drug;
2. It could not reasonably be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when a toxicity does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g. bone marrow depression, fixed drug eruptions, tardive dyskinesia);
4. It follows a known pattern of response to the test drug.

Definite (must have all four criteria)

This category applies to those toxicities that are felt to be incontrovertibly related to the test drug. A toxicity may be considered definitely related if and when:

1. It follows a reasonable temporal sequence from administration of the test drug;
2. It could not reasonably be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It disappears or decreases on cessation or reduction in dose with re-exposure to drug. (Note: this is not to be construed as requiring re-exposure of the subject; however, a category of definitely related can only be used when a recurrence is observed.)
4. It follows a known pattern of response to the test drug.

7 INSTITUTIONAL REPORTING REQUIREMENTS

7.1 Safety Reporting of Adverse Events and Serious Adverse Events

Adverse event reporting and definitions:

The NCI CTC Version 4.0 will be used. In the event of an adverse event the first concern will be for the safety of the subject.

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

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

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

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

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

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

Investigators are required to report to The Merck Drug Safety ANY serious treatment emergent adverse event (STEAE) that is study related as soon as possible.

A STEAE is any sign, symptom or medical condition that emerges during Aprepitant or Ondansetron treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of treatment or as part of the patient's medical history

but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

7.2 Reporting of Serious Treatment Emergent Adverse Events

Information about all serious adverse events will be collected and recorded on the FDA Medwatch 3500A form. To ensure patient safety each serious adverse event that is study related will also be reported to MERCK Drug Safety, preferably in writing by fax, within 24 hours of discovery by the Principal Investigator and sent to: Merck (Attn: Worldwide Product Safety; FAX 215 993-1220) with copies of all serious adverse experiences, within two working days regardless of drug relationship. Additionally, any pregnancy occurring in association with use of a Merck Product will be reported to Merck (Attn: Worldwide Product Safety; FAX 215 993-1220).

A copy of all 15 Day Reports and Annual Progress Reports will be submitted as required by FDA, if applicable, or other local regulators by the sponsor-investigator. Cross reference this submission according to local regulations, will be submitted to the Merck Investigational Compound number (IND, CSA, etc.) at the time of submission. Submitted copy of these reports will be sent to Merck (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to the appropriate regulatory agency.

Merck Drug Safety

Fax: 215-993-1220

(Please use the safety reporting fax cover sheet for your fax transmission)

AND:

Study Coordination Center/Principal Investigator

Contact Information and fax #:

Katherine B. Peters, MD, PhD

919-684-6173-phone

Mary Lou Affronti RN, MSN, ANP, MHSc

919-684-6239 phone

919-684-6674-fax

AND:

The Duke IRB

(eIRB system)

Mandatory MedWatch 3500A Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

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

- Adding to the original Mandatory MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A 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 MERCK may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported.

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that Aprepitant and/or Ondansetron caused or contributed to an adverse event. The following general guidance may be used.

Attribution of AEs will be indicated as follows:

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

8 STATISTICAL METHODS

8.1 Overview and Sample Size Justification

The objective of this study is to assess the efficacy of Aprepitant vs. Ondansetron in the prevention of chemotherapy induced nausea and vomiting in brain tumor patients treated with temozolomide +/- Avastin. The primary basis for this assessment will be the complete control rate (CC), defined as the proportion of patients with no emetic episode and no rescue medication during days 1-7.

A two-arm open-labeled randomized phase II screening trial is proposed in which 136 patients are randomized with equal probability to receive Ondansetron with or without Aprepitant. Patient randomization will be stratified by grade (I/II vs. III/IV) and the number of prior regimens (0/1 versus 2). Within each of the 4 strata defined by these factors, a permuted block randomization scheme will be used to assign patients to receive either Ondansetron with or without Aprepitant.

Though the study is comparative, the goal of the study is to determine whether Aprepitant is worthy of further investigation in this setting, and not to make definitive statements about the comparative effectiveness of Ondansetron treatment with or without Aprepitant. A control arm is included in this study design in lieu of historical controls to ensure that an appropriate comparison can be made without concern that the patients receiving standard treatment differ in some manner (Rubinstein, 2009; Ratain, 2009; Ratain, 2008)

Stupp (2005) reports that 19% of patients treated with temozolomide experience grade 2-4 vomiting. Given that the focus of this study is on the occurrence of such toxicity during days 1-7, it is reasonable to assume for sample size calculations that rate of CINV is approximately 14%, or CC rate of 86%. If the true CC rate associated with Aprepitant were comparable, there would be limited interest in further investigating the use of Aprepitant as a prophylactic treatment for CINV. However, if the true CC rate associated with Aprepitant were 96% or greater, there would be interest in pursuing further research with Aprepitant to determine the merits of integrating it use into standard treatment of glioma patients undergoing temozolomide treatment. The statistical hypothesis that will be assessed is as follows:

$$H_0: P_1 \leq P_2 \text{ versus } H_1: P_1 > P_2$$

where P_1 is the proportion of patients treated with Aprepitant who do not experience CINV (i.e. CC rate) and P_2 is the same proportion among patients not treated with Aprepitant.

As a phase II study, there is a need to constrain the sample size requirements at the expense of either an increased false negative or false positive rate. As proposed by Ratain and Sargent, a false-positive rate of 0.2 will be used to test this hypothesis. With 68 randomized patients per arm (total=136 patients) in this screening study, the power of a test conducted at the 0.2 level of significance is 0.9. This power was computed assuming that the CC rate in the two arms is 86% under the null hypothesis, and 86% and 96% under the alternative hypothesis.

An interim efficacy analysis will be conducted after 68 patients have been enrolled onto the study. If the observed proportion of patients treated with Aprepitant who do not experience CINV is less than that observed among patients not treated with Aprepitant, patient accrual will be terminated. With this interim analysis, simulation studies show that the type I and II error rates are 0.19 and 0.11, respectively. The probability that the study will be terminated early under the null hypothesis is 0.43, while the probability of early termination under the alternative hypothesis is 0.04.

8.2 Analytic Methods

Primary Analysis: The proportion of patients with no emetic episode or rescue medication during days 1-7, also referenced as the CC rate, will be estimated with a 95% confidence interval within each treatment arm. Logistic regression will be used to compare treatment arms with respect to the CC rate assuming a 0.2 level of significance.

Secondary Analyses: The acute CINV CR rate (i.e. for day 1) will be calculated, and a logistic regression model will compare treatment arms. The delayed CR rate (i.e. for days 2-7) will also be calculated with a logistic regression model comparing treatment arms.

The Cochran-Armitage Trend Test will be used to compare treatment arms with respect to the day of treatment failure of the antiemetic therapy.

Logistic regression will be used to examine the effect of treatment arm, age, gender, chemotherapy history, the use of glucocorticoids on the CCCR rate. Statistical interactions with arm will also be explored in this analysis.

The frequency of toxicity will be summarized by treatment arm, type and most severe grade experienced.

A generalized linear model for repeated measures will compare treatment arms with respect to the pattern over time for global satisfaction with antiemetic treatment and quality of life.

8.3 Toxicity Monitoring

If the percentage of patients with treatment-related grade 4 or 5 non-hematologic toxicity in the Aprepitant arm is greater than 5%, and that observed proportion is double the percentage of patients without Aprepitant with treatment-related grade 4 or 5 non-hematologic toxicity, then accrual will be suspended and the data carefully reviewed to determine if accrual should be permanently terminated.

9 STUDY MANAGEMENT: DATA SAFETY AND MONITORING PLAN

9.1 Audits and Inspections

Authorized representatives of the Institutional Review Board (IRB) or Duke Cancer Institute (DCI) may visit the center to perform audits or inspections, including source data verification. The purpose of such an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted,

and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

9.2 Study Monitoring Requirements

The DCI Safety Oversight Committee (SOC) conducts annual data and safety monitoring for DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent DSMB. Annual safety reviews include review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. Studies are rated satisfactory when adequate accrual with lack of excessive toxicity is present.

The sponsor-investigator provides the DCI Safety Oversight Committee (SOC) – Safety Report to the SOC annually, upon request, or the data may be submitted simultaneously with required reporting, e.g., FDA annual report. Attachments (e.g., accrual tables, toxicities and reference literature) are also acceptable for SOC review. The sponsor-investigator is notified in writing if additional information is needed and if protocol or operational changes are required. The SOC will notify the sponsor-investigator and DUHS IRB when significant safety concerns are identified. The SOC Chair has the authority to temporarily suspend accrual to the study pending acceptable changes. Any recommendation for temporary or permanent suspension of an NIH-funded clinical protocol will be reported by the sponsor-investigator via written communication to the responsible NCI grant program director.

9.3 Monitoring

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits as defined by DCI Cancer Protocol Committee (CPC), on DUHS sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements. The Monitoring Team also provides ongoing education and resources to investigators and study teams to enhance the quality.

As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. The frequency of monitoring may also be tailored as defined by the CPC. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI Leadership, the DCI CPC, the Safety Oversight Committee (SOC), the study supporter, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

This phase II study is limited to Duke University Medical Center. Routine monitoring by study investigators will review toxicity data including all SAEs and other issues relevant to the study such as interim assessment of accrual, outcome and compliance with study guidelines.

9.4 Audits

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

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

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

9.5 Data Collection

The PIs will be responsible for accurate, consistent, timely, complete and reliable data collection.

The study coordinator and PIs are responsible for ensuring that the following forms are completed in a legible and timely manner for every patient enrolled on study. These forms are an integral part of the study data and will be maintained in the patient’s clinical chart at the Brain Tumor Center at Duke (BTC). Errors on the forms should be lined through, but not obliterated, with the correction inserted, initialed and dated by the study coordinator or PIs. All source documents will be available for inspection by the FDA, DUHS IRB, and the Duke Cancer Institute Safety Oversight Committee. All source documents will be available at all times for inspection by the FDA, DUHS IRB, and the DCI SOC.

Patient data will be entered into an Oracle Clinical database created and maintained by Duke CCIS. The data are backed up daily and stored on a secure medical center server. The PIs,

study investigators, study statisticians, clinical research coordinator, and data coordinators for the study are the only individuals who will have access to the web-based Oracle application.

10 REFERENCES

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2. Aapro, M. S. (1993). Review of experience with ondansetron and granisetron. *Annals of Oncology*, *4 Suppl 3*, 9-14.
3. Aapro, M. S., Grunberg, S. M., Manikhas, G. M., Olivares, G., Suarez, T., Tjulandin, S. A., . . . Macciocchi, A. (2006). A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Annals of Oncology*, *17*(9), 1441-1449. doi: 10.1093/annonc/mdl137
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11 APPENDICES

11.1 CINV Patient Survey (MAT/Osoba)

Please see attached.

11.2 Cytochrome P450 Drug Interaction Table

Please see the following website, which is updated frequently as new information becomes available (Flockhart, 2007):

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

11.3 PK Sample Collection/Processing and Plasma Storage for Temozolomide and AIC Metabolite Analysis

Materials to be ready and ICE-COLD or REFRIGERATED ahead of time of sample collection:

1. 4-mL sodium heparin “green top” Vacutainer[®] tubes, ref# 367871 (1 ea.)
2. 2-mL polypropylene screw-cap tube containing 0.06 mL of 8.5% phosphoric acid (1 ea.) This tube will be clearly labeled “A.”
3. 1-mL polypropylene transfer pipettes (1 ea.)
4. 2-mL cryo-vials labeled “TEMO/AIC,” study #, patient study #, date and time of blood draw, as well as date and time of doses of aprepitant, ondansetron and temozolomide (2ea.). These tubes will be clearly labeled “B.”
- 5.

For **temozolomide/AIC** measurement, blood sample will be collected in pre-chilled (wet ice or refrigerated at 4 °C) sodium heparin “green top” Vacutainer[®] tube and immediately placed back on wet ice or refrigerated at 4 °C. The sample will be processed as soon as possible (within 60 minutes) by centrifugation (4°C, 1200 g, 10 min). The plasma will be transferred in tube labeled “A” (2 mL polypropylene (PP) screw-cap tube containing 0.06 mL of 8.5% phosphoric acid), mixed well, and content transferred into two equal (~1-mL ea.) aliquots using two tubes labeled “B” (“TEMO/AIC”-labeled 2-mL PP tubes), and immediately stored at -20°C (or lower) until the time of analysis.

11.4 Stupp Regimen (2005)

Radiation therapy administered as fractionated focal irradiation in daily fractions of 2Gy given 5 days a week for 6 weeks for a total of 60 Gy, or 1.8 Gy given 5 days a week for 33 treatments for a total of 59.4 Gy, and concomitant temozolomide 75 mg/m² daily (7 days per week) during radiotherapy.

External beam radiation (XRT) will begin 2-6 weeks after surgery and temozolomide 75 mg/m² daily will be started within the first 5 days of XRT. Beginning, a minimum of 2 weeks after the last radiation treatment, temozolomide will be given at 150 to 200 mg/m² daily the first 5 days of each 28-day cycle.

11.5 NCI CTC Toxicity Grading (Version 4.0)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

11.6 The Preston Robert Tisch Brain Tumor Center Clinical Research Team Standard Operating Procedure for Randomization of Aprepitant (Emend) Study

eIRB# Pro00031206: A Randomized Open Label Phase II Trial of Aprepitant (Emend) in Combination with Ondansetron Compared to Standard 5HT3 Serotonin Antagonist (Ondansetron) in the Prevention of Acute and Delayed Chemotherapy Induced Nausea and Vomiting (CINV) in Glioma Patients receiving a Temozolomide Based Regimen

Purpose: To provide standard operating procedures for randomizing subjects to the above clinical trial.

Scope: Statistical Team, Principal Investigator, Study Coordinator, DCI IT and ICS

Process:

As per the protocol, a permuted block randomization schema will be developed by team statistician and provided to DCI IT for REDcap development

- REDcap (via SAS) will randomize subjects to one of two treatment arms based on the following 2 factors that create 4 strata:
 1. Number of regimens
 - 0 or 1 regimens
 - 2 regimens
 2. Histologic grade
 - Grade 1 or 2
 - Grade 3 or 4
- Randomization date (the date that the randomization information is being entered)
- Subject is randomized to 1 of 2 Arms
 1. Arm A: Emend + Zofran
 2. Arm B: Zofran alone
- Data Management team and/or Statistical team will access treatment assignment information in REDcap and Oracle Clinical on a monthly basis to assess data quality and consistency
- A second research team member will verify that each subject has been randomized correctly when checking eligibility

Procedures:

1. CRC or designate assigns a subject ID Number on DOCR enrollment log when subject deemed protocol eligible
 - Study ID numbers to start with #101 and continues sequentially
2. CRC or designee enters the required stratification factors in Redcap to randomize subject and uses the assigned numbers sequentially per DOCR enrollment log
 - Number of regimens

- Histologic grade
 - Date of randomization
3. Arm A orders are processed and approved in DUHS electronic ordering system by BTC physician (EMEND only) and prescription provided to subject for Zofran
 4. Arm B Zofran prescription is provided by physician
 5. EMEND is dispensed from ICS if randomized to Arm A
 6. Randomization assignments sheets will be printed from REDcap to verify eligibility to Arm A or Arm B

Access to randomization data in Redcap is issued by DCI IT after the Investigator/designee approval:

1. CRC
 2. CRC identified backup
 3. Clinical Trials Manager
 4. Data Manager
 5. Statisticians – view only
 6. DCI IT
- * Refer to REDcap Randomization Project document for further information.