The Preston Robert Tisch Brain Tumor Center
Duke University Medical Center
A Phase II Study

Phase II randomized study to evaluate efficacy, patient satisfaction, and compliance of the oral combination of Rolapitant (Varubi®) plus ondansetron vs. ondansetron monotherapy in malignant glioma patients receiving radiotherapy (RT) and concomitant temozolomide

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Original version:	Date 11/29/16	
Amended version:	Date 01/12/17	Lead study coordinator changed, rolapitant dose (180 mg) added to study schema (Section 6) and study design (Section 9.1). Extensive information on past palonosetron study was removed in sections

	5.2, 7.1, and 7.3. A clarification of a total of 80 randomized patients for interim analysis was added to section 15.6. Primary endpoint and KEY secondary endpoint clarification to headings in section 15.7. Hyperlinks modified appropriately.
Date 8/8/17	Updated eligibility to include patients that may want to participate in a clinical trial AFTER standard of care radiation and temodar (Section 5.4 and 11.2). Removed redundant inclusion criteria (Section 5.4 and 11.1). Removed excess pregnancy tests (Table 7).
Date 2/19/18	Added ECOG to inclusion criteria, removed redundant radiotherapy criteria that is covered by the broad criteria – "prior cancer chemotherapy or radiotherapy" in exclusion criteria, removed urine pregnancy test from exclusion criteria because only serum pregnancy test will be used (Section 5.4 and 11). Removed SGOT from Inclusion Criteria #5 given that AST limits are set in Inclusion Criteria #6 (Section 11.1). Removed the "Xs" from the Adverse Events line and replaced it with continuous, added urinalysis, removed medication log from screening, increased screening period to 4 weeks, and added a footnote for Laboratory Evaluations at screening (Table 7). Added urinalysis to screening procedures text (Section 12.1). Removed the reference to only clinically significant abnormal lab findings will be recorded as Adverse Events because ALL abnormal laboratory findings will be recorded and then clinical significance will be decided (Section 13.1). Various new Adverse Event and other reporting criteria updated per new company standards (Section 13) including addition of an AESI section (Section 1.1.1). an SAE exception (Section 13.2), SEA reporting to Tesaro (Sections 13.2.1 and 1.1.1), a pregnancy section (Section 13.3.2.1), Special Situations (Section 1.1.1), and Reporting Product Complaints (Section 1.1.1). Removed Karen Allen and Gordana Vlahovic from Sub-Investigators. Added Margaret Johnson to sub-investigators. Changed Lead Study Coordinator to Edy Parker and Lead Regulatory Coordinator to Jennifer Jackman. Some minor administrative edits.
Date 1/31/19	Changed Lead Regulatory Coordinator to Deborah Iden. Updated all references of Tesaro to TerSera, the new sponsor. Exclusion criteria #1 removed and combined with #2 to indicate that co-medication interaction with rolapitant will be reviewed by the pharmacist for eligibility and added exclusion criteria for contraindicated medications (Sections 5.4 and 11.2). Added a sentence after exclusion criterion 18 that says to refer to a study Memo to File for exceptions to the exclusion criteria. (Sections 5.4 and 11.2) Reordered the Inclusion and Exclusion criteria numbering to better lend itself to how the questions are reviewed when screening by the CRC. Removed collection of every 2 week standard of care blood draw at the request of the PI who determined it was unnecessary to collect the data (Table 7) and throughout the protocol. Section 13, Safety Monitoring and Reporting, was significantly revised to both include language suggested by the new sponsor TerSera and to remove sections that had only been included based on the previous sponsor's requirements. Corrected inconsistencies in the language related to screening time points. Removed overall duration of study. Other minor administrative changes.
Date 2/18/2022	The accrual target for this study is reduced to 57 patients. The decision to terminate early has not been influenced by the data collected to date, as no interim analyses have been conducted. The analyses as described below will be conducted; however, they may no longer have the power to detect the hypothesized effect size

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$5HT_3$-RA	5-hydroxytryptamine receptor antagonist
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&P	History & Physical Exam
HEC	Highly emetic chemotherapy
HRPP	Human Research Protections Program
IV (or iv)	Intravenously
MASCC	Multinational Association of Supportive Care in Cancer
MAT	MASCC Antiemesis Tool
MEC	Moderately emetic chemotherapy
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCCN	National Comprehensive Caner Network
NK_1-RA	Neurokinin-1 receptor antagonist
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PET	Positron Emission Tomography
PD	Progressive Disease
PFS	Progression Free Survival
PRTBTC	Preston Robert Tisch Brain Tumor Center
p.o.	per os/by mouth/orally
RT	Radiation Therapy
RINV	Radiation Induced Nausea and Vomiting
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TSQM-9	Treatment Satisfaction Questionnaire for Medication
WBC	White Blood Cells

5 PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

5.1 Purpose

The purpose of this two-arm randomized phase 2 study is to assess the efficacy and patient satisfaction of oral rolapitant plus ondansetron vs. oral ondansetron *monotherapy* in malignant glioma (MG) patients receiving six weeks of standard cranial radiation therapy (RT) and concomitant temozolomide (TMZ).

Primary Objective:

1. Compare the efficacy of rolapitant plus ondansetron vs. ondansetron mono therapy in the prevention of chemoradiation-induced nausea and vomiting (chemo-RINV), as measured by the overall complete response (CR) rate (where CR is defined as no emesis, no rescue antiemetic), among malignant glioma patients during the standard ~ 6 weeks of RT and concomitant multi-dose TMZ

Secondary Objectives:

1. KEY secondary objective: Assess whether malignant glioma patients receiving RT and concomitant TMZ are more satisfied with rolapitant plus ondansetron vs. ondansetron monotherapy for the prevention of chemo-RINV
2. Describe the rationale behind a patient's satisfaction with antiemetic preference based upon effectiveness, convenience and global satisfaction
3. Compare the efficacy of rolapitant plus ondansetron vs. ondansetron monotherapy in the prevention of nausea and vomiting separately, as measured by the respective CIN, CIV -CR rates, among malignant glioma patients during RT and concomitant TMZ
4. Evaluate compliance of rolapitant plus ondansetron vs. ondansetron monotherapy
5. Assess the safety of rolapitant plus ondansetron vs. ondansetron monotherapy in the prevention of RINV in glioma patients receiving RT and concomitant TMZ

Hypotheses

1. This is a hypothesis-testing protocol. Hypothesis: rolapitant plus ondansetron will produce an equally or a more effective RINV CR rate when compared to ondansetron monotherapy in glioma patients receiving RT and concomitant TMZ.

5.2 Background and Significance

Radiation-induced nausea and vomiting (RINV) is a clinically distressing symptom in patients undergoing radiotherapy. The RINV risk in patients receiving cranial/cranio spinal radiation without concurrent chemotherapy is estimated to be around 30-60%.[1] Although there is limited evidence to suggest that the RINV incidence is higher with the addition of temozolomide to RT than without, one would only predict that the incidence of RINV without emetic prophylaxis among patients treated with combination therapy (i.e. radiation and concurrent temozolomide) is higher. In two recent clinical studies, 35% or more of cranial RT patients experienced RINV.[2,3] The risk of RINV increases when concomitant chemotherapy with TMZ is added to brain RT,[4] as TMZ is moderately emetogenic.[5,6] Temozolomide prescribing information reports nausea and vomiting rates of 36% and 20% respectively for concomitant RT+TMZ and concomitant RT+TMZ with standard antiemetic treatment.[7] Comparable rates of nausea (35%) and vomiting (26%) were reported in a recent study of Korean MG patients receiving such treatment.[8] The National Comprehensive Cancer Network (NCCN), Multinational Association of Supportive Care in Cancer (MASCC), and American Society of Clinical Oncology (ASCO) publish current clinical practice guidelines addressing the issue of RINV [9,10,6] and these guidelines recommend that patients receiving concomitant chemotherapy and RT treatment should be given antiemetic prophylaxis according to the emetogenicity of the chemotherapy prescribed, unless the emetic risk of the radiotherapy is higher. Given the moderate emetogenicity of TMZ therapy, patients with brain tumors are classified as a moderate-risk group for RINV.

At Duke PRTBTC, we estimate the RINV rate to be approximately 50% without the use of ondansetron. Despite prophylaxis against nausea and vomiting during cranial RT and concomitant temozolomide therapy, Stupp [4,11]

reported a threefold (14% - 40/287) increase in the grade 2-4 nausea/vomiting rate compared to a 4% (11/286) nausea/vomiting rate with radiotherapy alone. Without prophylaxis, up to 60% of patients receiving cranial radiation may experience acute nausea and vomiting, which can lead to various adverse effects including dehydration, electrolyte imbalance, malnutrition, and aspiration pneumonia. These complications can further delay/decrease the therapeutic effect of temozolomide and radiation treatment, ultimately leading to lower response rates and decreased health-related quality of life (HRQoL).

We conducted the first phase 2 single arm trial of palonosetron (PAL), a long acting 5-hydroxytryptamine (5-HT_3) receptor antagonist ($5HT_3$-RA), for the prevention of RINV in primary MG subjects receiving RT (54-60 Gy) and concomitant multi-dose, daily TMZ (75 mg/m^2) +/- bevacizumab. Results from this study demonstrate that a $5HT_3$-RA, such as PAL or ondansetron, can be safe and effective, however based on the results, there is still room for improvement of anti-emetic response related to CR rates and HRQoL, which could be addressed by combining a 5-HT_3-RA and NK-1-RA[12]. PAL was safe and effective; however, there is room for improvement in the CR rates and HRQoL, which may be achieved with rolapitant plus ondansetron, a potentially more effective combination anti-emetic regimen. The most studied agents in the RINV settings are the $5HT_3$-RAs, with overall moderate response and low toxicity. However, agents such as the tachykinin NK-1 receptor antagonist may play a role in improving response rates, but there needs to be further studies in randomized controlled trials.[13]

Rolapitant, an FDA-approved, long-acting, highly selective NK_1 receptor antagonist (RA), in combination with a 5-HT_3 RA (ondansetron, granisetron) and dexamethasone is a well-tolerated antiemetic combination that has demonstrated superiority for the prevention of highly-emetic chemotherapy induced nausea and vomiting (CINV)[14]. In a global, randomized, double-blind, active-controlled, phase 3 multi-center study, 1369 patients receiving moderately-emetic chemotherapy or regimens containing an anthracycline and cyclophosphamide were randomly allocated (after stratification by sex) to receive either one 180 mg dose of oral rolapitant or a placebo (active control) 1-2 hours before administration of chemotherapy. All patients also received granisetron (2 mg orally) on days 2-3 and dexamethasone (20 mg orally) on day 1[15], on cycles of a minimum of 14 days. The primary efficacy endpoint was complete response (CR indicated by no emesis or rescue medication) during the delayed (>24-120 hours) phase. A significantly larger proportion of patients receiving rolapitant had complete responses in the delayed phase than did those receiving active control (475 [71%] vs 410 [62%]; odds ratio 1.6, 95% CI 1.2-2.0; p=0.0002).[15] Toxicities were similar in the rolapitant and control groups, with the most frequently reported treatment-related treatment-emergent adverse events being fatigue, constipation, and headache.[15] No serious adverse event was treatment-related, and no treatment-related adverse event resulted in death.[15]

The oral combination of rolapitant plus ondansetron has not been studied in the prevention of RINV in patients receiving RT and multi-dose chemotherapy for MG. Additional advantages to using rolapitant plus ondansetron in the setting of radiation with concurrent multi-dose oral chemotherapy are that it avoids side effects associated with intravenous administration (e.g. palonosetron) and eliminates treatment room costs. Furthermore, rolapitant, as opposed to the aprepitant or netupitant, is not a CYP3A4 inhibitor or inducer of common drugs used in glioma patients (e.g. dexamethasone, enzyme-inducing anticonvulsants, or irinotecan) thus reducing drug-induced side effects. **Ultimately, rolapitant plus ondansetron may improve overall efficacy (CR rates), cost, HRQoL and patient satisfaction.**

5.3 Design and Procedure

This proposed study is a randomized phase 2 trial of rolapitant plus ondansetron vs. ondansetron monotherapy for the prevention of chemo-RINV in primary malignant glioma subjects receiving radiation therapy (RT) and concomitant multi-dose temozolomide (TMZ). All eligible subjects should receive a planned total dose of 54-60 Gy of radiation and 75 mg/m^2 of temozolomide daily for a total of six weeks. Glioma patients will be randomized in an unblinded fashion to receive one of two treatment sequences of antiemetic therapy for the prevention of nausea and vomiting associated with RT and concomitant TMZ.

Sequence A involves administration of ondansetron alone for 3 weeks followed by the use of rolapitant X 1 dose plus daily ondansetron for 3 weeks; whereas, sequence B involves the use of rolapitant X 1 dose plus daily ondansetron for 3 weeks followed by 3 weeks of daily ondansetron alone. For the rolapitant plus ondansetron weeks (1 or 4), patients will self-administer the oral rolapitant pill 1-2 hours before the first fraction of radiation on the planned week (see schema). Subjects will be given a prescription for ondansetron 8 mg pills to be taken 30 minutes before their TMZ dose. After the start of radiation therapy, the type of additional rescue antiemetic medication, if needed, will be left up to the investigator's discretion. Subjects will be informed that they are allowed to take rescue antiemetic medication while participating in either arm of the study. If the subject experiences nausea and vomiting and does take a rescue antiemetic, the subject will be asked to record the use of additional antiemetic in a medication log provided to them. Subjects will complete weekly medication logs and surveys (see Appendices) to capture study outcomes. Subjects will be told that the study is voluntary and that they may exit at any time if they wish.

Approximately 170 patients will provide informed consent in order for 160 patients to be randomized to either treatment sequence A or B. The 170 estimate is to allow for screen failures and dropout rates. All subjects must give written informed consent to participate in the study. Patients will be screened -28 to 0 days prior to the start of the study. During this time period the following information will be recorded: physical examination; vital signs and weight; laboratory studies (complete blood count with differential, blood chemistries, liver function tests and urinalysis): medical history; concomitant medications (steroids and anticonvulsants) and predictors of RINV (irradiation site, planned dose treatment field, alcohol intake, gender, age etc.). Laboratory evaluations, performance status, concomitant medications, and adverse events for final eligibility should be confirmed within 2 weeks of initiating radiation with concomitant TMZ

Patients will obtain standard of care blood work (per local oncologistduring treatment complete blood count with differential, blood chemistries, liver function tests). Toxicity will be assessed based on the Common Toxicity Criterion (CTC version 4). The patient will be asked to complete the MASCC nausea and vomiting questionnaire on day 0 (baseline), and days 1, 2, 4, and 7 (for days 7, 1, 2-3, and 4-6, respectively) of each week of radiation therapy.

At the end of weeks 3 & 6, the subject will be asked to fill out a Treatment Satisfaction Questionnaire for Medication (TSQM-9, Section 18.1 and 18.2) and will be asked at the end of week 6 to choose which antiemetic they prefer.

5.4 Selection of Subjects

Selection of Subjects: Patients with a malignant glioma who plan to undergo standard RT with concomitant daily temozolomide (TMZ) therapy

Inclusion Criteria:

1. Patients must have histologically-confirmed, newly-diagnosed malignant glioma (glioblastoma, gliosarcoma, anaplastic astrocytoma, anaplastic oligoastrocytoma, anaplastic pleomorphic xanthoastrocytoma, or anaplastic oligodendroglioma) and are scheduled to receive radiotherapy (for a total of 54-60 Gy) and concomitant daily temozolomide therapy (at a dose of 75 mg/m^2 for one complete 6-week cycle).
2. Age ≥ 18 years
3. Karnofsky ≥ 60% or ECOG 0-2
4. For patients on higher than physiological level of corticosteroids, they must have been on a stable dose for 1 week prior to initiating study drug, and the dose should not be escalated over entry dose level, if clinically possible
5. Ability and willingness to give informed consent
6. Female patients of childbearing potential must have a negative pregnancy test at Screening
7. Female patients of childbearing potential must agree to use an acceptable method of birth control (please refer to the attached document, Birth Control Recommendations (Appendix 18.5)) from the signing of

informed consent form and to continue its use during the study and for at least 90 days after the final dose
8. Male patients must agree to use an acceptable form of birth control (please refer to the attached document, Birth Control Recommendations (Appendix 18.5) from study Day 1 through at least 90 days after the final dose
9. Hematocrit ≥29%, ANC ≥1,000 cells/mm^3, platelets ≥100,000 cells/ mm^3
10. Serum creatinine ≤1.4 mg/dl, bilirubin <1.5 times upper limit of normal
11. Aspartate aminotransferase (AST) ≤2.5 x upper limit of normal range (ULN). For subjects with known liver metastases ≤5 x ULN, and alanine aminotransferase (ALT) ≤2.5 x ULN. For subjects with known liver metastases ≤5 x ULN

Exclusion Criteria:
1. Co-medications that may interact with rolapitant as reviewed by Duke Preston Robert Tisch Brain Tumor investigator pharmacist
2. Co-medications that are contraindicated in patients on rolapitant including pimozide, thioridazine, carbamazepine, colchicine, dabigatran (Pradaxa), edoxaban (Savaysa), fosphenytoin, metoprolol, phenobarbital, phenytoin, primidone, and warfarin
3. Inability or unwillingness to cooperate with the study procedures
4. Prophylactic medication for the **prevention** of nausea and vomiting 24 hours prior to the start of radiation therapy through the full course of radiation therapy is prohibited, with the exception of the study drug. Corticosteroids will be allowed for treatment of cerebral swelling
5. Ongoing vomiting from any organic etiology
6. Previous participation in any clinical trial involving rolapitant
7. Received rolapitant within 21 days prior to study enrollment
8. Prior cancer chemotherapy or radiotherapy
9. Any current treatment, medical history, or uncontrolled condition, other than malignancy, (e.g., alcoholism or signs of alcohol abuse, seizure disorder, medical or psychiatric condition) that, in the opinion of the investigator, would confound the results of the study or pose any unwarranted risk in administering study drug to the subject
10. Patient has a known hypersensitivity to the administration of rolapitant or its excipients
11. Patient has a history of severe renal or hepatic impairment, severe bone marrow suppression, or systemic infection
12. Patient is a woman with a positive serum pregnancy test at Screening, is pregnant, breast-feeding, or is planning to conceive children within the projected duration of the study treatment
13. Patient has taken the following agents within the last 48 hours prior to the start of treatment with study drug:
    - 5-HT_3 antagonists (ondansetron, granisetron, dolasetron, tropisetron, etc.).
    - Benzamides (metoclopramide, alizapride, etc.)
    - Domperidone
    - Cannabinoids
    - NK1 antagonist (aprepitant)
    - Benzodiazepines (lorazepam, alprazolam, etc.)
    - herbal medications or preparations in doses designed to ameliorate nausea or emesis
14. Patient has taken phenothiazines (prochlorperazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine, etc.) for any indication within the last 48 hours prior to the start of treatment with study drug
15. Palonosetron is not permitted within 7 days prior to administration of investigational product
16. Any vomiting, retching, dry heaves, or clinically significant nausea (i.e., NCI Common Toxicity Criteria version 4.0 grade 2-4 nausea) caused by any etiology in the 24 hrs. preceding day 1 of the study intervention (ondansetron or ondansetron with rolapitant) as scheduled to begin on day 1 of radiation and chemotherapy. Or a patient who has a history of anticipatory nausea and vomiting.

17. Patient must not have been dosed with test drug or blinded study drug in another investigational study within 30 days or 5 half-lives of the biologic activity of the test drug, whichever is longer, before the time of first study dose
18. Patient who is receiving investigational agent(s) as part of another clinical study at the time of screening or who anticipates receiving investigational agent(s) during their scheduled radiotherapy and concomitant daily temozolomide therapy. (Please refer to study Memo to File regarding exceptions to this exclusion criteria)

5.5 Subject Recruitment and Compensation

Subjects will be recruited for this study as follows:

Subjects will be identified from patients referred to the Preston Robert Tisch Brain Tumor Center Clinic. Upon determination that a subject's tumor histology and radiographic findings are compatible with the eligibility criteria for this study protocol, the study will be briefly explained to the subject by the clinical research coordinator (CRC) or Mary Lou Affronti DNP, RN, MSN, ANP, MHSc, or Dr. Katherine Peters, the principal investigators (PIs), or a member of the research team in the PRTBTC (may include RNs, CRCs, MDs or advanced practice providers). If the subject indicates interest in study participation, study education sheets will be provided by the research nurse clinicians as this provides the most comprehensive explanation of the study in lay terms. If the patient shows continued interest, the PI or member of the research study staff will thoroughly explain the required elements of informed consent and all aspects of the study to the subject including but not limited to inclusion/exclusion criteria, risks, benefits, and alternatives to study participation. If the patient desires additional time to consider participation in the study, the study staff will send the patient home with the consent form. If the patient takes the consent form home and decides to participate, a return appointment to the PRTBTC will be scheduled with the study nurse and study coordinator to complete the informed consent process face to face with the patient.

No compensation for participation will be given to subjects. The study medication, rolapitant, is FDA-approved and will be provided at no charge by the study supporter, TerSera. A third party insurance carrier will be responsible for the cost of clinic visits, laboratory tests, dexamethasone, and routine care and treatment for the brain tumor (including ondansetron and rescue medication). How much subjects will have to pay, depends on whether or not they have insurance or what costs the insurance will cover. Insurance coverage cannot be guaranteed for all tests and treatments related to this study. Treatment to help control side effects may also result in added costs.

5.6 Consent Process

Subjects must give informed consent according to institutional review board (IRB) guidelines prior to registration. The subject will receive a copy of the signed consent document. The original signed consent document will be retained by the PRTBTC in a study binder. The PI or designee will fully explain the purpose and potential risks and benefits of the study to the subject prior to enrollment and address any questions posed by the subject. In addition, the PI or designee will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any additional discomfort that may be anticipated from taking this antiemetic drug combination. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The prospective participant will have as much time as he/she may need to make an informed decision about the study, and all treatment-related questions will be answered. Prospective participants will be consented in an exam room where only the research staff, the patient, and his/her family (if desired) are present. Before, during, and after the consent process, the research team and investigators will be available in person and by phone to answer any questions the participants may have. Any and all other available treatment options are

offered to the patient in order to avoid undue influence. Participants are not offered compensation for this study, in order to avoid any monetary coercion/influence.

For those prospective participants who cannot read or are blind, the consent document will be read out loud verbatim to the participant, who is encouraged to have a caregiver or family member present as a witness who can read along as the consent form is read. If the prospective participant cannot read or understand English, an approved, translated, short form consent document will be provided to the participant. A translator and a translator/witness, along with the Brain Tumor Center attending physician, nurse, or coordinator, will review the short form consent document and the full English version of the consent and all relevant study documents with the subject. If a subject has a physical impairment that limits their ability to provide a signature, an impartial witness will be utilized as part of the informed consent process. This impartial witness will date and sign the Informed Consent along with the person obtaining the informed consent.

5.7 Subject's Capacity to Give Legally Effective Consent

Subjects participating in this study are competent to sign informed consent, based upon inclusion criteria and investigator assessment. Subjects who do not have the capacity to give legally effective consent will not be enrolled.

5.8 Risk/Benefit Assessment

The natural progression of this type of brain tumor and standard treatment modalities are associated with potentially life-threatening complications and side effects. The antiemetic study drug (rolapitant) may increase the risk of side effects.

Table 1: The study of drug, Varubi® (rolapitant) with MEC can cause the following effects:

	VARUBI Regimen (VARUBI, Dexamethasone, and 5-HT_3 Receptor Antagonist) N = 670	**Control (Placebo, Dexamethasone, and 5-HT_3 Receptor Antagonist) N = 674**
Decreased appetite	9%	7%
Dizziness	6%	4%
Dyspepsia	4%	2%
Urinary tract infection	4%	3%
Stomatitis	4%	2%

Allergic reactions may occur rarely. Hives; tightness of the throat; difficulty breathing or swallowing; hoarseness should be reported to the study doctor immediately.

Note: The Reference Safety Information for the study will be the United States Package Insert (USPI).

Ondansetron
Most common side effects (occurring in 9 to 24% of subjects):

- Headache
- Fatigue
- Constipation

Side effects occurring in 5-6% of subjects:

- Diarrhea
- Dizziness

Other side effects that have been reported by people who have taken ondansetron (intravenous [by vein] or by mouth) in clinical studies include the following:

- Low oxygen level in the blood (Hypoxia)
- Fever
- Slow heart rate (Bradycardia)
- Urinary retention
- Itching
- Drowsiness/sedation
- Shivers

Serotonin syndrome has been reported when ondansetron has been taken at the same time as another medication that affects serotonin, a type of neurotransmitter (a chemical produced by the body). Such medications include certain types of anti-depressants and migraine medications. The study team will review your list of medications with you to find out if you are taking any of these medications. Please seek immediate medical attention if you experience any of the following symptoms of serotonin syndrome: changes in mental status, autonomic instability (this could include fainting or dizziness, exercise intolerance, sweating too much or too little, difficulty with urinating, sexual problems, and visual problems), neuro-muscular symptoms, and gastrointestinal symptoms, such as loss of appetite, bloating, diarrhea, constipation, or difficulty swallowing.

Other medications:

Subjects should tell the study doctor about all drugs that they have been taking recently and are taking while enrolled in this study. Also, if a severe side effect occurs, the study doctor may permanently stop the study drug. Subjects must tell their study doctor and research staff of their concern of any of these side effects, as listed above.

5.9 Costs to the Subject

The study drug, rolapitant, is FDA-approved and will be provided at no charge. Ondansetron is commercially available and will not be covered by the study. The subject or their third party insurance carrier will be responsible for the cost of his/her clinic visits, laboratory tests, dexamethasone (as needed), and the routine care and treatment of their brain tumor, e.g. the radiation therapy and temozolomide. How much one will have to pay, depends on whether or not the subject has insurance and those costs that his/her insurance will cover. Insurance coverage cannot be guaranteed for all tests and treatments related to this study. Treatment to help control any side effects that may occur may also result in added costs to the subject or their insurance company. Subjects will not be paid for taking part in this study.

5.10 Duration of Study

Participants will be in the study for 8 weeks which includes ~6 weeks of treatment and 2 weeks of monitoring for adverse events following the end of radiation and concurrent temozolomide treatment.

5.11 Data Analysis and Statistical Considerations

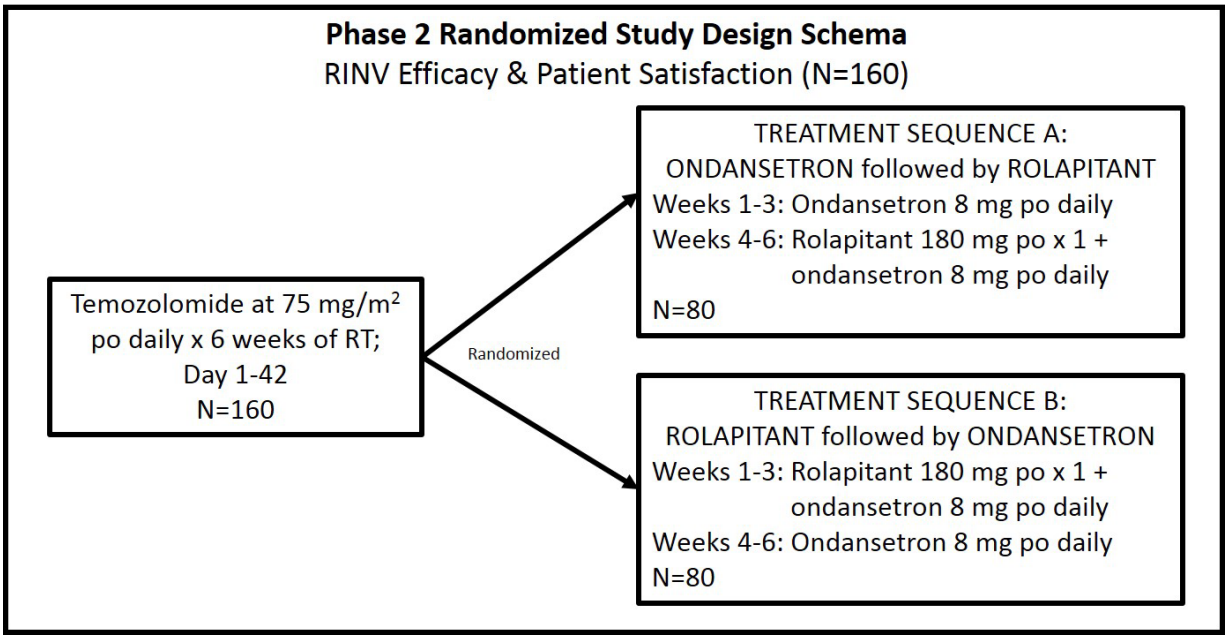
One hundred seventy (170) glioma patients will be enrolled with the expectation that 160 patients will be randomized (unblinded) to receive one of two treatment sequences of anti-emetic therapy for the prevention of nausea and vomiting associated with RT and concomitant TMZ. Sequence A involves a 3-week regimen of daily ondansetron followed by a 3-week regimen consisting of rolapitant (day 22 only) and daily ondansetron; whereas, Sequence B involves a 3-week regimen of rolapitant (day 1 only) and daily ondansetron followed by a 3-week regimen of daily ondansetron.

The primary endpoint of this study is CR rate. Though the primary CR rate endpoint will focus on treatment during the first 2 weeks of RT and TMZ, a cross-over design is proposed so that a patient will experience both modes of treatment, and be equipped to make a comparative assessment of preference, which is a key

secondary outcome. An interim analysis (as described in 15.6) will be conducted by the study statistician or designee after 40 patients are accrued to each sequence.

We expect that 152 of the 160 randomized patients to provide an assessment of their experience during the first 2 weeks of treatment with the first regimen. With 152 patients, there is 80% power to detect an increase in the CR rate from 75% with ondansetron to 90% with the combination of ondansetron and rolapitant (α=0.05; one-tailed) with a chi-square test.

6 STUDY SCHEMA



7 BACKGROUND AND SIGNIFICANCE

7.1 Study Disease

Radiation-induced nausea and vomiting (RINV) is a clinically distressing symptom in patients undergoing radiotherapy. The RINV risk in patients receiving cranial/craniospinal radiation without concurrent chemotherapy is estimated to around 30-60%.[1] Although there is limited evidence to suggest what the RINV incidence is higher with the addition of temozolomide to RT than without, one would only predict that the addition of concurrent chemotherapy with brain irradiation would only increase the RINV rate. In two recent clinical studies, 35% or more of cranial RT patients experienced RINV.[2,3] The risk of RINV increases when concomitant chemotherapy with TMZ is added to brain RT,[4] as TMZ is moderately emetogenic.[5,6] Temozolomide prescribing information reports nausea and vomiting rates of 36% and 20% respectively for concomitant RT+TMZ and concomitant RT+TMZ with standard antiemetic treatment.[7] Comparable rates of nausea (35%) and vomiting (26%) were reported in a recent study of Korean malignant glioma patients receiving such treatment.[8] The National Comprehensive Cancer Network (NCCN), Multinational Association of Supportive Care in Cancer (MASCC), and American Society of Clinical Oncology (ASCO) publish current clinical practice guidelines addressing the issue of RINV [9,10,6] These guidelines recommend that patients receiving concomitant chemotherapy and RT treatment should be given antiemetic prophylaxis according to the emetogenicity of the chemotherapy prescribed, unless the emetic risk of the radiotherapy is higher. Given the moderate emetogenicity of TMZ therapy, patients with brain tumors are classified as a moderate-risk group for RINV.

At Duke PRTBTC, we estimate the RINV rate to be approximately 50% without the use on ondansetron. Despite prophylaxis against nausea and vomiting during cranial RT and concomitant temozolomide therapy, Stupp [4,11] reported a threefold (14% - 40/287) increase in the grade 2-4 nausea/vomiting rate compared to a 4% (11/286) nausea/vomiting rate with radiotherapy alone. Without prophylaxis, up to 60% of patients receiving cranial radiation may experience acute nausea and vomiting, which can lead to various adverse effects including dehydration, electrolyte imbalance, malnutrition, and aspiration pneumonia. These complications can further delay/decrease the therapeutic effect of temozolomide and radiation treatment, ultimately leading to lower response rates and decreased health-related quality of life (HRQoL).

We conducted the first phase 2 single arm trial of palonosetron (PAL), a long acting 5-hydroxytryptamine (5-HT_3) receptor antagonist ($5HT_3$-RA), for the prevention of RINV in primary MG subjects receiving RT (54-60 Gy) and concomitant multi-dose, daily TMZ (75 mg/m^2) +/- bevacizumab. Results from this study demonstrate that a $5HT_3$-RA, such as PAL or ondansetron, can be safe and effective, however based on the results, there is still room for improvement of anti-emetic response related to CR rates and HRQoL, which could be addressed by combining a 5-HT_3-RA and NK-1-RA[12]. PAL was safe and effective; however, there is room for improvement in the CR rates and HRQoL, which may be achieved with rolapitant plus ondansetron, a potentially more effective combination anti-emetic regimen. Additionally, PAL is only available as an IV injection in the United States whereas ondansetron can be administered orally, making it a more patient-friendly drug. The most studied agents in the RINV settings are the $5HT_3$-RAs, with overall moderate response and low toxicity. However, agents such as the tachykinin NK-1 receptor antagonist may play a role in improving response rates, but there needs to be further studies in randomized controlled trials.[13]

7.2 Study Agent

Rolapitant, an FDA-approved, novel, long-acting, new highly-selective neurokinin-1 (NK_1) receptor antagonist (RA), in combination with a $5HT_3$-RA (i.e. ondansetron, granisetron) and dexamethasone is a well-tolerated antiemetic combination that has demonstrated superiority for the prevention of highly-emetic chemotherapy (HEC) induced nausea and vomiting (CINV)[14].

In a global, randomized, double-blind, active-controlled, phase 3 multi-center study, 1369 patients receiving moderately-emetic chemotherapy (MEC) or regimens containing an anthracycline and cyclophosphamide were randomly allocated (after stratification by sex) to receive either one 180 mg dose of oral rolapitant or a

placebo (active control) 1-2 hours before administration of chemotherapy. All patients also -received granisetron (2 mg orally) and dexamethasone (20 mg orally) on day 1 and granisetron (2 mg orally) on days 2-3.[15] The median cycle duration was 21 days with the recommended minimum dosing for Rolapitant at no less than 14 day intervals. The primary efficacy endpoint was complete response (CR: no emesis, no rescue medication) during the delayed (>24-120 hours) phase. A significantly larger proportion of patients receiving rolapitant had complete responses in the delayed phase than did those receiving active control (475 [71%] vs 410 [62%]; odds ratio 1.6, 95% CI 1.2-2.0; p=0.0002).[15] Toxicities were similar in the rolapitant and control groups, with the most frequently reported treatment-related treatment-emergent adverse events being fatigue, constipation, and headache.[15] No serious adverse event was treatment-related, and no treatment-related adverse event resulted in death.[15]

Mechanism of action: Rolapitant is a selective and competitive antagonist of human substance P/NK_1 receptors. Rolapitant does not have significant affinity for the NK_2 or NK_3 receptors or for a battery of other receptors, transporters, enzymes and ion channels. Rolapitant is also active in animal models of chemotherapy-induced emesis.

Pharmacodynamics: NK_1 Receptor Occupancy - A Human Positron Emission Tomography (PET) study with rolapitant demonstrated that rolapitant crosses the blood brain barrier and occupies brain NK_1 receptors. A dose-dependent increase in mean NK_1 receptor occupancy was observed in the dose range from 4.5 mg to 180 mg of rolapitant. At the 180 mg dose of rolapitant, the mean NK_1 receptor occupancy was 73% in the striatum at 120 hours after a single dose administration in healthy subjects. The relationship between NK_1 receptor occupancy and the clinical efficacy of rolapitant has not been established.

Cardiac Electrophysiology - In a thorough QT study, rolapitant at doses up to 4 times higher than the recommended dose had no significant effects on the QT intervals

Pharmacokinetics: Absorption - Following a single dose administration of 180 mg rolapitant under fasting conditions to healthy subjects, rolapitant was measurable in plasma between 30 minutes and the peak plasma concentration (C_{max}) for rolapitant was reached in about 4 hours, and mean C_{max} was 968ng/mL (%CV:28%). Following multiple oral doses 9 to 45 mg once daily of rolapitant; accumulation of rolapitant was approximately 5-fold. The systemic exposures (C_{max} and AUC) to rolapitant increased in a dose-proportional manner when the dose of rolapitant increased from 4.5 mg to 180 mg. With an increase in dose by 4 times from the recommended clinical dose of 180 mg, the C_{max} and AUC of rolapitant increased by 3.1 fold and 3.7 fold, respectively. Concomitant administration of a high fat meal did not significantly affect the pharmacokinetics of rolapitant after administration of 180 mg rolapitant.

Distribution - Rolapitant was highly protein bound to human plasma (99.8%). The apparent volume of distribution (Vd/F) was 460 L in healthy subjects, indicating an extensive tissue distribution of rolapitant. In a population pharmacokinetic analysis of rolapitant, the Vd/F was 387 L in cancer patients.

Elimination - Following single oral doses (4.5 to 180 mg) of rolapitant, the mean terminal half-life ($t_{1/2}$) of rolapitant ranged from 169 to 183 hours (approximately 7 days) and was independent of dose. In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of rolapitant was 0.96L/hour in cancer patients.

Metabolism - Rolapitant is metabolized primarily by CYP3A4 to form a major active metabolite, M19 (C4-pyrrolidine-hydroxylated rolapitant). In a mass balance study, the metabolite M19 was the major circulating metabolite. The formation of M19 was significantly delayed with the median T_{max} of 120 hrs. (range: 24-168 hours) and the mean half-life of M19 was 158 hours. The exposure ratio of M19 to rolapitant was approximately 50% in plasma.

Excretion - Rolapitant is eliminated primarily through the hepatic/biliary route. Following administration of a single oral 180 mg dose of [^{14}C]-rolapitant, on average 14.2% (range 9% to 20%) and 73% (range 52% to 89%)

of the dose was recovered in the urine and feces, respectively over ~ 6 weeks. In pooled samples collected over 2 weeks, 8.3% of the dose was recovered in the urine primarily as metabolites and 37.8% of the dose was recovered in the feces primarily as unchanged rolapitant. Unchanged rolapitant or M19 were not found in pooled urine sample.

Specific Populations - Age, Sex and Race/Ethnicity - Population pharmacokinetic analyses indicated that age, sex and race had no significant impact on the pharmacokinetics of rolapitant.

Pregnancy: There are no available data on rolapitant use in pregnant women to inform any drug-associated risks. In animal reproduction studies, there were no teratogenic or embryo-fetal effects observed with oral administration of rolapitant hydrochloride in rats and rabbits during the period of organogenesis at doses up to 1.2 times and 2.9 times, respectively, the maximum recommended human dose (MRHD). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and15% to 20%, respectively.

Hepatic Impairment- Following administrations of a single dose of 180 mg rolapitant to patients with mild hepatic impairment (Child-Pugh Class A), the pharmacokinetics of rolapitant were comparable with those of healthy subjects. In patients with moderate hepatic impairment (Child-Pugh Class B), the mean C_{max} was 25% lower while mean AUC of rolapitant was similar compared to those of healthy subjects. The median T_{max} for M19 was delayed to 204 hours in patients with mild or moderate hepatic impairment compared to 168 hours in healthy subjects. The pharmacokinetics of rolapitant was not studied in patients with severe hepatic impairment (Child-Pugh Class C).

Renal Impairment- In population pharmacokinetic analyses, creatinine clearance (CLcr) at baseline did not show a significant effect on rolapitant pharmacokinetics in cancer patients with mild (CLcr: 60 to 90 mL/min) or moderate (CLcr: 30 to 60 mL/min) renal impairment compared to cancer patients with normal kidney function. Information is insufficient for the effect of severe renal Impairment. The pharmacokinetics of rolapitant was not studied in patients with end-stage renal disease requiring hemodialysis.

Drug Interaction Studies-Effect of Other Drugs on Rolapitant - Rolapitant is a substrate for CYP3A4.

CYP3A4 inducers - Concomitant administration of a CYP3A4 inducer significantly decreased the systemic exposure to rolapitant. When 600 mg rifampin (CYP3A4 inducer) was administered once daily for 7 days before and 7 days after administration of a single dose of 180 mg rolapitant, the mean C_{max} of rolapitant was reduced by 30% and the mean AUC was reduced by 85% compared to administration of rolapitant alone. The mean half-life of rolapitant decreased from 176 hours without rifampin to 41 hours with concurrent rifampin. Strong CyP3A4 inducers (e.g., rifampin) significantly reduced plasma concentrations of rolapitant, which can decrease the efficacy of rolapitant; avoid use of rolapitant in patients who require chronic administration of such drugs.

CYP3A4 inhibitors: No clinically significant effect was seen on the pharmacokinetics of rolapitant when ketoconazole, a strong CYP3A4 inhibitor was administered with rolapitant. Concurrent administration of 400 mg ketoconazole once daily for 21 days following a single 90 mg dose of rolapitant, did not significantly affect the C_{max} of rolapitant while the AUC increased by 21%.

Effect of Rolapitant on Other Drugs – Effects of rolapitant on CYP450 enzymes and transporters is summarized below:

CYP3A4 substrates: Rolapitant is neither an inhibitor nor an inducer of CYP3A4, therefore, no dosage adjustment for dexamethasone (CYP3A4 substrate) is needed when co-administered with rolapitant.

Dexamethasone: Rolapitant had no significant effects on the pharmacokinetics of dexamethasone when oral dexamethasone was administered days 1-3 after a single 180 mg dose of rolapitant was co-administered on Day 1.

Ondansetron: Rolapitant had no significant effects on the pharmacokinetics of intravenous ondansetron when concomitantly administered with a single 180 mg dose of rolapitant on the same day.
CYP2D6 inhibitor:
Rolapitant is a (1) moderate inhibitor of CYP2D6 (i.e. concomitant use with Thioridazine is contraindicated due to QT prolongation and Torsa des de Pointes. Avoid use of rolapitant with pimozide,); (2) an inhibitor of Breast-Cancer-Resistance Protein-BCRP (i.e. Topetecan, Methotrexate; Use the lowest effective dose of rosuvastatin), and (3) an inhibitor of P-glycoprotein (P-gp) (increased plasma concentrations of digoxin, or other P-gp substrates, may result in potential adverse reactions. Monitor for increased digoxin concentrations). Refer to package insert. The Table below is a summary of the effects of the clinical dose of rolapitant on the pharmacokinetics of co- administered drugs:

Table 2: Effects of Rolapitant on the Pharmacokinetics of Co-administered Drugs*

Enzyme/ transporter	Co-administered drug	% Change for Co-Administered Drug Day 1 with rolapitant		Day 8 without rolapitant	
		Change in C_{max}	Change in AUC	Change in C_{max}	Change in AUC
CYP2D6	Dextromethorphan 30mg	120% ↑	160% ↑	180% ↑	230% ↑
BCRP	Sulfasalazine 500 mg	140% ↑	130% ↑	17% ↑	32% ↑
P-gp	Digoxin 0.5 mg	70% ↑	30% ↑	n/a	n/a

* A single dose of 180 mg rolapitant was administered on day 1; the interacting drug was administered on day 1 with rolapitant and alone on day 8; ↑ Denotes an average increase in exposure by the percentage indicated. n/a: Not studied

Rationale for use in gliomas: The oral combination of rolapitant plus ondansetron has not been studied in the prevention of RINV using *multi-dose* chemotherapy in individuals with malignant glioma. Additional advantages to using rolapitant plus ondansetron in the setting of radiation with concurrent multi-dose oral chemotherapy are that it avoids side effects associated with intravenous administration (e.g. palonosetron) and eliminates treatment room costs. Furthermore, rolapitant, as opposed to the aprepitant or netupitant, is not a CYP3A4 inhibitor or inducer of for common drugs used in glioma patients (e.g. dexamethasone, enzyme-inducing anticonvulsants, or irinotecan) thus reducing drug-induced side effects. The NK_1 antagonist EMEND® (aprepitant) was approved by the US Food and Drug Administration and by the European Medicines Agency for the prevention of acute and delayed CINV associated with highly emetic chemotherapy (HEC- i.e. high dose cisplatin) and MEC when used in combination with a 5-HT_3 antagonist and a corticosteroid. Dosage adjustment of concomitantly administered drugs is necessary with aprepitant, which is a mixed inducer/inhibitor of cytochrome P450 (CYP) 3A4 and also affects other CYP enzymes. Rolapitant has been free of clinically relevant drug interactions in studies conducted to date, has rapid and good brain penetration, which may contribute to its quick onset of action, and a long half-life that allows for dosing only once during each cycle of chemotherapy. PET occupancy studies as well as clinical efficacy data support the use of only a single dose of rolapitant to protect patients for 5 days from CINV. Rolapitant has been selected as a promising agent to address this and other shortcomings of existing therapy. **Ultimately, rolapitant plus ondansetron may improve overall efficacy (CR rates), cost, HRQoL and patient satisfaction.**

7.2.1 Pre-clinical experience (as noted in the Rolapitant Investigator's brochure)

Rolapitant has been evaluated in a series of non-clinical toxicity studies of up to 6 months duration in rats and up to 9 months duration in monkeys by oral administration and up to 14 days duration in rats and up to 1 month duration in monkeys by intravenous (IV) infusion. Developmental and reproductive toxicity studies, genetic toxicity studies, and safety pharmacology studies were also conducted. In addition, genetic toxicity studies and a safety pharmacology study were conducted with the pharmacologically active metabolite SCH720881. Furthermore, 2-year oral carcinogenicity studies of rolapitant in rats/mice have been completed.

Major findings in the non-clinical toxicity studies reported to date are convulsions in rats, mice, and monkeys at high lethal or near lethal doses (oral administration) and in monkeys (after IV infusion) as well as developmental and reproductive findings in female rats. For convulsions, exposure margins have been identified in the non-clinical species relative to clinical exposure data at an oral dose of 200 mg and there has been no evidence of treatment- related seizures in the completed clinical trials. Since the rolapitant clinical development program has not nor will include women who are pregnant or attempting to become pregnant, the findings in the developmental and reproductive studies in rats are not considered relevant for the CINV clinical trials. The mouse carcinogenicity study with rolapitant was negative; the rat carcinogenicity study showed a non-significant increase in thyroid follicular cell tumors and benign adrenal medullary tumors.

7.2.2 Clinical experience (as noted in the Rolapitant Investigator's brochure and the package insert)

The total number of subjects exposed to oral rolapitant is approximately 2,800 which include 1,567 CINV patients and 1,231 healthy volunteers or patients from several additional Phase 1 and Phase 2 studies. Rolapitant was well tolerated at single doses up to 800 mg or as a once- daily dose up to 50 mg for 10 days. Orally administered rolapitant was completely bioavailable, rapidly absorbed, and slowly cleared. Maximum concentrations of a 200 mg dose were approximately 1000 ng/mL and were achieved by approximately 4 hours. The half-life was approximately 170 hours (average), suggesting that a single dose may be sufficient to prevent CINV during both the acute and delayed phases of CINV. Rolapitant is highly bound to plasma proteins, with an unbound (free) fraction of <1%. Urinary excretion of the dose is minor, and the major route of elimination is via the feces. Rolapitant is extensively metabolized by oxidation, primarily to SCH 720881, an equipotent human NK_1 RA. The formation and elimination of SCH 720881 are slow.

In phase 1 drug interaction studies, administration of rolapitant did not alter the pharmacokinetics of midazolam, dexamethasone or ondansetron, drugs metabolized by cytochrome P450 3A4. This indicates lack of a clinically relevant inhibition of CYP3A4 by rolapitant. Moreover, the PK of repeated doses of dexamethasone was also unaffected by a single 200 mg oral dose of rolapitant, indicating a lack of significant CYP3A4 induction by rolapitant or its metabolite. Inhibition of CYP3A4 by concomitant agents is unlikely to affect the PK of single doses of rolapitant, since concentrations of both rolapitant and the active metabolite SCH 720881 were unaffected by repeated daily oral doses (400 mg) of the potent CYP3A4 inhibitor ketoconazole.

Repeated administration of daily rifampin 600 mg (as 2 x 300 mg), a strong CYP3A4 inducer, was observed to induce the metabolism of rolapitant (4 x 50 mg) such that a 1.5-fold reduction in C_{max} and a 6- to 8-fold reduction in $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were observed along with a reduction in half-life from 176 hrs. to 41 hours.

Co-administration of a single 200 mg oral dose of rolapitant with a single 0.5 mg oral dose of digoxin led to increases in C_{max} and $AUC_{0\text{-}96h}$ values for digoxin by 71% and 30%, respectively. No clinically

meaningful effects on pharmacodynamic responses to digoxin were observed; therefore, rolapitant may have modest effects as an inhibitor of P-glycoprotein (P-gp).

In a recently conducted drug interaction study to assess the effect of rolapitant on the pharmacokinetics of specific probe substrates, preliminary results indicate that rolapitant inhibited the metabolism of dextromethorphan, a CYP2D6 substrate, and sulfasalazine, a BCRP substrate suggesting that rolapitant is a mild to moderate inhibitor of these enzymes. Therefore, dosage adjustments may be warranted for sensitive CY2D6 substrates and/or BCRP transporter substrates when given concomitantly with rolapitant, Rolapitant did not, however, alter the pharmacokinetics of tolbutamide, omeprazole, efavirenz or repaglinide, drugs metabolized by CYP2C9, CYP2C19, CYP2B6, or CYP2C8 respectively. In a recently conducted PK study in subjects with impaired hepatic function, preliminary results indicate comparable rolapitant PK profiles were observed in subjects with mild hepatic impairment and a slight decrease in exposure with subjects with moderate hepatic impairment when compared to healthy subjects. Therefore, dose adjustment for rolapitant when administered to patients with mild to moderate hepatic impairment is not required. Subjects with severe hepatic impairment were not evaluated in this study.

A human ECG study demonstrated no effects of rolapitant 200 mg or 800 mg (4 times the therapeutic dose) on the QTc interval. A clinical PET study demonstrated that single oral doses of rolapitant ranging from 5 to 200 mg can block the occupancy of cortical NK_1 receptors by the selective PET ligand^{11} C-GR205171. After a 200 mg dose, over 90% of central NK_1 receptors remained blocked for at least 5 days.

A multicenter, randomized, double-blind, active- and placebo-controlled Phase 2 study was conducted in patients undergoing surgical procedures to evaluate the effect of rolapitant monotherapy at doses of 5 to 200 mg for the prevention of PONV post-anesthesia. Response rates for the primary endpoint (no emetic episodes during the first 24 hrs. post-operatively increased with increasing rolapitant dose, with maximum response rate of 86.5% in the rolapitant 200-mg group. Subjects administered rolapitant doses of 20, 70, or 200 mg were significantly more likely to have no emetic episodes for 0 to 24 hrs. than subjects given placebo, and the level of significance was dose related. In this study there was no pattern of dose or treatment dependency in the incidence of AEs. The most common (≥10% of subjects) treatment-emergent AEs were constipation, headache, pruritus, postoperative GI disorder, hypotension, and dizziness. A total of 90 subjects (17%) in the active treatment groups experienced AEs that were considered at least possibly or probably related to treatment compared with 17 (17%) of 103 placebo subjects. There were no appreciable safety concerns and no dose-related effects noted in clinical laboratory, vital sign, or ECG data.

In study P04351 a dose range-finding phase 2 study was conducted in 454 patients receiving HEC (≥70 mg/m^2 cisplatin-based chemotherapy). The primary objective was to demonstrate that administration of rolapitant, at doses between 10 and 200 mg, along with ondansetron and dexamethasone, reduced the incidences of both acute and delayed CINV. A dose-response trend was generally observed for all efficacy endpoints, including complete response (defined as no emetic episodes and no rescue medication), no emesis, no nausea, no significant nausea, total control, and complete protection (defined as no emesis, no rescue medication, and maximum nausea VAS <25 mm on a 0 to 100 mm scale). For the 200 mg group, the overall (0-120 hrs.) complete response rate was 62.5% compared with 46.7% for placebo ($p = 0.032$). For the acute phase, the response rate was 87.6% vs. 66.7% ($p = 0.001$); for the delayed phase, the response was 63.6% vs. 48.9% ($p = 0.045$). At lower rolapitant dosage levels, complete response rates did not achieve statistical significance. The rolapitant 200 mg dose group also demonstrated significantly greater rates of no emesis and no significant nausea in the overall, acute and delayed phases than the control group. Kaplan-Meier curves comparing time to first event showed separation from control starting before 6 hrs. which represents a quicker onset of action that has been demonstrated with other agents in its class.

In this dose range-finding study the incidences of treatment-emergent adverse events (AE) and serious adverse events (SAE) were similar across all treatment groups. The most common (≥10% of subjects) treatment-emergent adverse events in the active treatment groups were nausea, fatigue, vomiting, constipation, and diarrhea. Overall, SAEs occurred in 52 (11%) of 454 randomized subjects during Cycle 1 of chemotherapy. The most common (≥1% of subjects) SAEs were febrile neutropenia, neutropenia, vomiting, dehydration, nausea, pneumonia, and renal failure. All SAEs were considered unlikely related to treatment except for one occurrence each of dizziness (10-mg dose group), elevated blood creatinine (100-mg dose group), and convulsions (100-mg dose group) which were considered by the investigator to be at least possibly related to treatment. Confounders for dizziness and elevated creatinine were concomitant chemotherapy and for convulsion was a previous history of convulsions and hyponatremia at the time of the event. The incidence of study drug discontinuation because of AEs was similar across treatment groups and ranged from 2% to 7%. Results from clinical laboratory tests, measurements of vital signs, and ECGs showed no appreciable safety concerns and no dose-related effects.

The results from the dose range-finding study showed rolapitant administered as a single dose of 200 mg with a 5-HT_3 receptor antagonist and dexamethasone to be highly effective in the prevention of CINV following HEC, together with data from the Phase 1 PET study, led to the dose selection and design of three global multicenter, randomized, parallel-group, double-blind, active-controlled phase 3 studies conducted in subjects receiving HEC (P04832 and Study P04833) and in subjects receiving MEC (Study P04834).

These studies were designed to evaluate the efficacy of a single dose of rolapitant 200 mg administered orally with granisetron and dexamethasone compared to placebo administered with granisetron and dexamethasone for the prevention of delayed phase CINV (>24 to 120 hrs.). The primary endpoint of all three studies was achieved. Specifically, the proportion of subjects who had no emesis and no use of rescue medication during the delayed phase of CINV, following initiation of HEC or MEC, was significantly higher for subjects receiving rolapitant compared with subjects receiving placebo (71.4% vs. 60.9%, respectively, $p < 0.001$). Likewise, the proportion of subjects who had no emesis and no use of rescue medication was significantly higher for subjects receiving rolapitant compared with subjects receiving placebo during the acute phase (< 24 hrs.) (83.5% vs. 78.7%, respectively, $p = 0.003$) and during the overall phase (0-120 hrs.) (68.7% vs. 58.1%, respectively, $p < 0.001$). Multiple secondary and tertiary endpoint comparisons favored the rolapitant group in the individual studies and in the pooled analyses and contribute additional support for the benefit of rolapitant during the delayed, acute and overall at risk period (0 to 120 hrs.) for patients receiving emetogenic chemotherapy. In addition, rolapitant was safe and well tolerated. No AEs were clearly attributable to administration of rolapitant. Neurological and other clinical /laboratory examinations did not detect specific safety signals ascribed to rolapitant.

A single ascending dose (SAD) and multiple ascending dose (MAD) assessment study of intravenous rolapitant in healthy volunteers was completed. The study's primary objective was to assess the safety and tolerability of intravenous (IV) rolapitant. A total of 57 subjects with a similar mean age of 37 years across each dose group were enrolled into Part 1 (SAD) and a total of 20 subjects with a similar mean age of 38 years across each dose group were enrolled into Part 2 (MAD).

Part 1 evaluated the safety and tolerability of intravenous rolapitant administered as a single ascending dose (20, 50, 100, 150, 185 and 200 mg) over 30 or 45 minutes. Intravenous (IV) rolapitant administered as a single ascending dose of up to 200 mg was well tolerated. There were no TEAEs resulting in death or SAEs reported in this study. All TEAEs were mild or moderate and had a single occurrence. The majority of TEAEs resolved spontaneously. No dose-dependent adverse events were observed, as indicated by the similarity of incidences of treatment-emergent and treatment-related emergent AEs among the different dose groups.

Part 2 evaluated the safety/tolerability of intravenous rolapitant administered as a multiple ascending doses (20, 40, and 60 mg) over 30 minutes. Intravenous (IV) rolapitant of 60 mg IV administered for 10

days was well tolerated. There were no serious TEAEs or TEAEs resulting in death and no TEAEs leading to discontinuation of dosing or discontinuation in this study. TEAEs were primarily mild and resolved spontaneously. Infusion-related adverse events, when they occurred, were generally mild, limited to the catheter site (mild pain or erythema), resolved and required only ice pack or removal of the IV and were most likely associated with the placement and manipulation of catheters, and PK sampling. There were no clinically significant laboratories, vital signs, physical or ECG findings in any of the subjects overall or within each dose group.

Rolapitant Efficacy in the CINV prevention

The efficacy of rolapitant for the prevention of CINV was initially evaluated in a phase 2, dose range-finding study (Study P04351). In this study, a statistically significant improvement in the primary efficacy endpoint of complete response (CR) (defined as no vomiting and no use of rescue medication during the overall 120-hour phase of CINV following initiation of chemotherapy) was observed in the rolapitant 200 mg group compared to control. Further, a statistically significant greater proportion of subjects in the rolapitant 200 mg group achieved CR in the acute and delayed phases compared with control. As further support to the effectiveness of rolapitant in the treatment of CINV following HEC, a statistically significant difference in the rates of emesis and no significant nausea were observed in all 3 phases compared to control. The results of this study, together with data from the phase 1 PET study led to the dose selection and design of three phase 3 studies, including two studies conducted in subjects receiving HEC (Study P04832 and Study P04833) and one conducted in subjects receiving MEC (Study P04834).

All three phase 3 studies were designed to evaluate the efficacy of a single dose of rolapitant 200 mg administered orally with granisetron and dexamethasone compared to placebo administered with granisetron and dexamethasone for the prevention of delayed phase CINV (>24 to 120 hrs.). Studies P04832 and P04833 were conducted in subjects receiving HEC (i.e., that receiving ≥60 mg/m^2 and Study P04834 was conducted in subjects receiving MEC.

The primary endpoint of all three phase 3 studies was achieved. Specifically, the proportion of subjects who did not experience emesis or use rescue medication during the delayed phase, >24 through 120 hrs., following initiation of HEC or MEC, was significantly higher for subjects receiving rolapitant compared with subjects receiving control. Multiple secondary and tertiary endpoint comparisons favored the rolapitant group in all studies and further support the benefit of rolapitant during the entire at risk period (0-120 hrs.) for patients receiving HEC or MEC. Efficacy findings for rolapitant were shown to be generalizable across multiple subgroups including gender, region, age, and race, and receipt of concomitant emetogenic chemotherapy. The Kaplan-Meier curve depicting time to first emesis or use of rescue medication which suggests that rolapitant provides a protective effect in the acute phase, with separation of the curves occurring early after administration of chemotherapy. This separation continues to increase during both the acute and delayed phases. In addition, the impact of rolapitant in reducing the negative effects of CINV on daily life, was clearly indicated by the higher proportion of subjects treated with rolapitant who reported less impact on daily life with respect to both the vomiting and nausea domains of the FLIE.

In conclusion, rolapitant demonstrated statistically and clinically meaningful prevention of CINV across four global, adequate, well-controlled clinical studies and the findings support an indication for rolapitant, when used in combination with a 5-HT$_3$-RA and dexamethasone, for the prevention of nausea and vomiting associated with initial and repeat courses of HEC or MEC. The studies enrolled a broad population of subjects based on age, gender, race and region with considerable comorbidities who were undergoing myelosuppressive chemotherapy for a variety of cancers. A summary of results for complete response by CINV Phase are presented in **Table 3**.

Table 3: Complete Response by CINV Phase and Study

Study Endpoint[a]	Rolapitant n / N (%)	Control n / N (%)	Rolapitant 200 mg vs. Control	
			Odds Ratio (95% CI)[b]	P-value[b]
Complete Response – Delayed Phase				
HEC (P04351)	56/ 88 (63.6)	44/ 90 (48.9)	1.9 (1.0, 3.4)	0.045
HECs Pooled	382/ 535 (71.4)	322/ 535 (60.2)	1.6 (1.3, 2.1)	<0.001
HEC (P04832)	192/ 264 (72.7)	153/ 262 (58.4)	1.9 (1.3, 2.7)	<0.001
HEC (P04833)	190/ 271 (70.1)	169/ 273 (61.9)	1.4 (1.0, 2.1)	0.043
MEC (P04834)	475/ 666 (71.3)	410/ 666 (61.6)	1.6 (1.2, 2.0)	<0.001
HECs/MEC Pooled [c]	857/1201 (71.4)	732/1201 (60.9)	1.6 (1.3, 1.9)	<0.001
Complete Response – Acute Phase				
HEC (P04351)	78/ 89 (87.6)	60 /90 (66.7)	3.6 (1.7, 7.8)	0.001
HECs Pooled	447/ 535 (83.6)	410/ 535 (76.6)	1.6 (1.1, 2.1)	0.004
HEC (P04832)	221/ 264 (83.7)	193/ 262 (73.7)	1.8 (1.2, 2.8)	0.005
HEC (P04833)	226/ 271 (83.4)	217/ 273 (79.5)	1.3 (0.8, 2.0)	0.233
MEC (P04834)	556/ 666 (83.5)	535/ 666 (80.3)	1.2 (0.9, 1.6)	0.143
HECs/MEC Pooled [c]	1003/1201 (83.5)	945/1201 (78.7)	1.4 (1.1, 1.7)	0.003
Complete Response – Overall Phase				
HEC (P04351)	55/ 88 (62.5)	42/ 90 (46.7)	1.9 (1.1, 3.5)	0.032
HECs Pooled	368/ 535 (68.8)	313/ 535 (58.5)	1.6 (1.2, 2.0)	<0.001
HEC (P04832)	185/ 264 (70.1)	148/ 262 (56.5)	1.8 (1.3, 2.6)	0.001
HEC (P04833)	183/ 271 (67.5)	165/ 273 (60.4)	1.4 (1.0, 1.9)	0.084
MEC (P04834)	457/ 666 (68.6)	385/ 666 (57.8)	1.6 (1.3, 2.0)	<0.001
HECs/MEC Pooled [c]	825/1201 (68.7)	698/1201 (58.1)	1.6 (1.3, 1.9)	<0.001

Abbreviations:

CI=confidence interval; CMH=Cochran-Mantel Haenszel; HEC=highly emetogenic chemotherapy; MEC=moderately emetogenic chemotherapy.

[a] Complete response is defined as no emesis or use of rescue medication.

[b] P04351: Odds ratio, CI and p-value are from logistic regression model with effects for treatment, concomitant emetogenic chemotherapy, and sex. P04832, P04833, P04834: Odds ratio, CI and p-value are from the CMH test adjusted for study (where studies are pooled) and gender effect.

[c] HECs/MEC Pooled=P04832, P04833, P04834.

Summary of Three Robust Clinical Studies

In two multicenter, randomized, double-blind, parallel group, controlled clinical studies (Study 1 and Study 2), the rolapitant (VARUBI) regimen (VARUBI, granisetron and dexamethasone) was compared with control therapy (placebo, granisetron and dexamethasone) in patients receiving a HEC chemotherapy regimen that included cisplatin >60 mg/m^2. See **Table 4** for the treatment regimens.

Table 4: Treatment Regimens in Studies 1 and 2

	Day 1	Day 2 to 4
VARUBI Regimen		
Oral VARUBI †	180 mg	none
Oral Dexamethasone	20 mg ‡	8 mg twice daily
Intravenous Granisetron	10 mcg/kg §	none
Control Regimen*		
Oral Dexamethasone	20 mg ‡	8 mg twice daily
Intravenous Granisetron	10 mcg/kg §	none

* VARUBI placebo was used to maintain blinding
† VARUBI was administered 1 to 2 hrs. prior to chemotherapy treatment on Day 1
‡ Dexamethasone was administered 30 minutes prior to chemotherapy on Day 1. There is no drug interaction between VARUBI and dexamethasone, so no dosage adjustment for dexamethasone required
§ The dose of granisetron was administered 30 minutes prior to chemotherapy on Day 1.

Study 1

A total of 532 patients were randomized to either the rolapitant (VARUBI) regimen (N =266) or control therapy (N =266). A total of 526 patients were included in the evaluation of efficacy. Of those randomized 42% were women, 58 % men, 67% White, 23% Asian, 1% Black, and 9% multi-racial/other/unknown. The proportion of patients from North America was 16%. Patients in this clinical study ranged from 20 to 90 years of age, with a mean age of 57 years. In Study 1, 26% of patients were 65 years or older, with 3% of patients being 75 years or older. The mean cisplatin dose was 77 mg/m^2. During this study, 82% of the patients received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common concomitant chemotherapeutic agents administered during Cycle 1 were: gemcitabine (17%), paclitaxel (12%), fluorouracil (11%), etoposide (10%), vinorelbine (9%), docetaxel (9%), pemetrexed (7%), doxorubicin (6%) and cyclophosphamide (5%).

Study 2

A total of 555 patients were randomized to either the rolapitant (VARUBI) regimen (N =278) or control therapy (N =277). A total of 544 patients were included in the evaluation of efficacy. Of those randomized 32% were women, 68 % men, 81% White, 14% Asian, 1% Black, and 5% multi-racial/other/unknown. The proportion of patients from North America was 7%. Patients in this clinical study ranged from 18 to 83 years of age, with a mean age of 58 years. In this study, 27% of patients were 65 years or older, with 3% of patients being 75 years or older. The mean cisplatin dose was 76 mg/m^2. During this study, 85% of the patients received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common concomitant chemotherapy agents administered during Cycle 1 were: vinrorelbine (16%), gemcitabine (15%), fluorouracil (12%), etoposide (11%), pemetrexed (9%), docetaxel (7%), paclitaxel (7%), epirubicin (5%) and capecitabine (4%).

The primary endpoint in both studies was complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hrs.) of CINV.

Study 3

In Study 3, a multicenter, randomized, double-blind, parallel group, controlled clinical study in moderately emetogenic chemotherapy (MEC), the rolapitant (VARUBI) regimen (VARUBI, granisetron and dexamethasone) was compared with control therapy (placebo, granisetron and dexamethasone) in patients receiving a moderately emetogenic chemotherapy regimen that included at least 50% of patients receiving a combination of anthracycline and cyclophosphamide. The percentage of patients who received carboplatin in Cycle 1 was 30%. Treatment regimens for the VARUBI and control arms are summarized in **Table 5**.

Table 5: Treatment Regimens in Study 3

	Day 1	Day 2 to 4
VARUBI Regimen		
Oral VARUBI†	180 mg	none
Oral Dexamethasone	20 mg‡	none
Oral Granisetron	2 mg§	2 mg once daily
Control Regimen*		
Oral Dexamethasone	20 mg‡	none
Oral Granisetron	2 mg§	2 mg once daily

* VARUBI placebo was used to maintain blinding
† VARUBI was administered 1 to 2 hrs. prior to chemotherapy treatment on Day 1
‡ Dexamethasone was administered 30 minutes prior to chemotherapy on Day 1.
§ The dose of granisetron was administered 30 minutes prior to chemotherapy on Day 1.

A total of 1369 patients were randomized to either the rolapitant (VARUBI) regimen (N = 684) or control therapy (N = 685). A total of 1332 patients were included in the evaluation of efficacy. Of those randomized 80% were women, 20% men, 77% White, 13% Asian, 4% Black, and 6% multi-racial/other/unknown. The proportion of patients from North America was 33%. Patients in this clinical study ranged from 22 to 88 years of age, with a mean age of 57 years. In this study, 28% of patients were 65 years or older, with 7% of patients being 75 years or older. The primary endpoint was complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hrs.) of chemotherapy-induced nausea and vomiting. A summary of the study results from HEC Studies 1 & 2, and for the MEC Study 3 is shown in **Table 6**.

Table 6: Percent of Patients Receiving Emetogenic Chemotherapy Responding by Treatment Group for the HEC Studies 1 and 2 and for the MEC Study 3

Endpoint	HEC Study 1			HEC Study			MEC Study 3		
	VARUBI† (N=264) Rate (%)	Control† (N=262) Rate (%)	P-Value Treatment Difference (95% C.I.)	VARUBI† (N=271) Rate (%)	Control† (N=273) Rate (%)	P-Value Treatment Difference (95% C.I.)	VARUBI† (N=666) Rate (%)	Control† (N=666) Rate (%)	P-Value Treatment Difference (95% C.I.)
Primary Endpoint: Complete Response in the Delayed Phase	72.7	58.4	<0.001* 14.3 (6.3,22.4)	70.1	61.9	0.043* 8.2 (0.3, 16.1)	71.3	61.6	<0.001* 9.8 (4.7, 14.8)

† Granisetron and dexamethasone were used as concomitant drugs.
* Results were obtained based on the Cochran-Mantel-Haenszel test stratified by gender.

Multiple-Cycle Extension: In Studies 1, 2, and 3, patients had the option of continuing into a multiple-cycle extension for up to 5 additional cycles of chemotherapy receiving the same treatment as assigned in cycle 1. At day 6 to 8 following initiation of chemotherapy, patients were asked to recall whether they had any episode of vomiting or retching or nausea that interfered with normal daily life. The results are summarized by study and treatment group in the figure below.

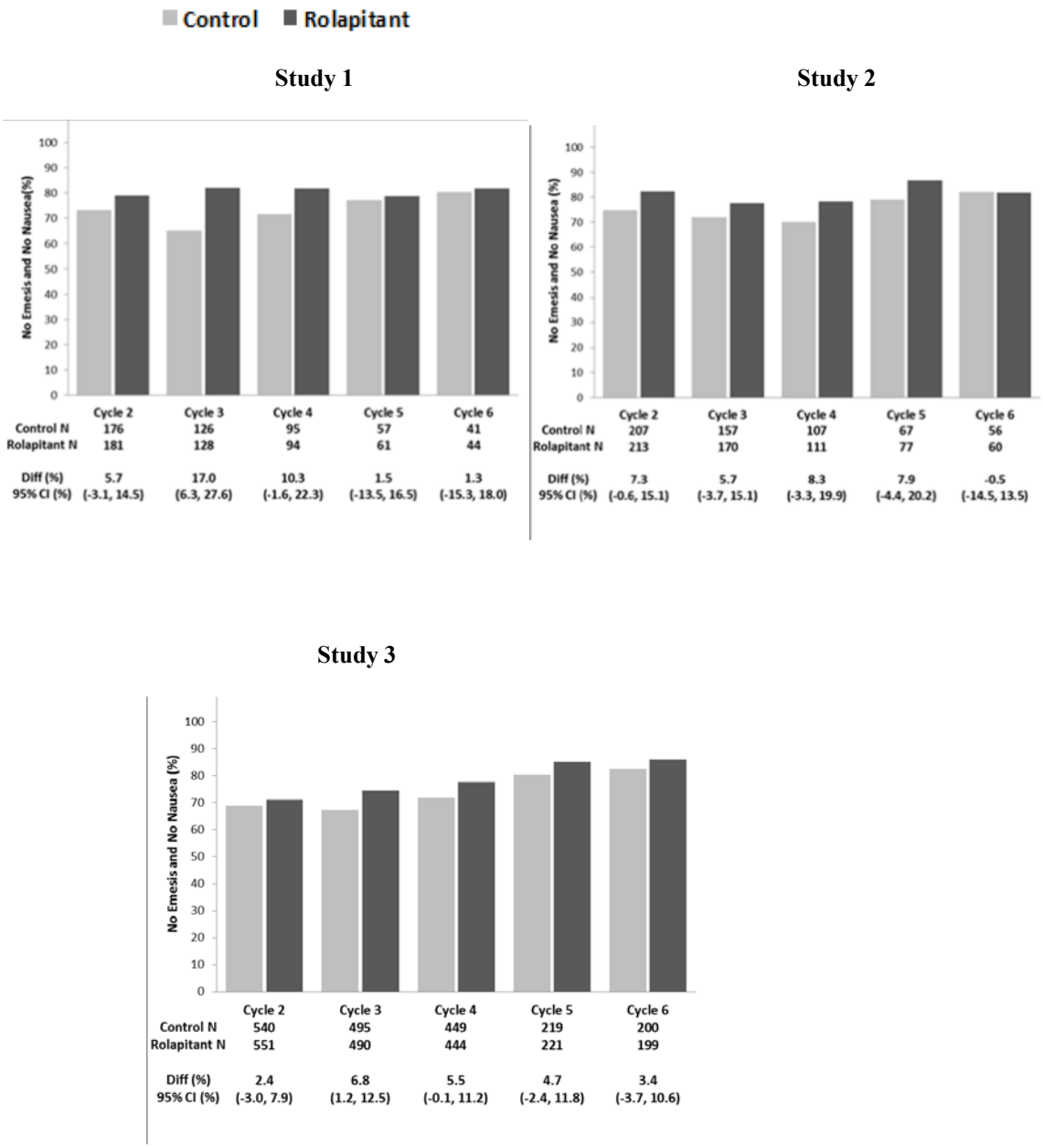


Figure 1: No Emesis and No Nausea Interfering with Daily Life over Cycles 2-6

7.3 Study Purpose/Rationale

The purpose of this randomized study is to primarily assess efficacy, in addition to patient preference, patient satisfaction and patient compliance of rolapitant plus ondansetron vs. ondansetron monotherapy for the prevention of chemo-radiation-induced nausea and vomiting (chemo-RINV) in malignant glioma patients receiving standard RT and concomitant TMZ (Stupp regimen).

We conducted the first phase 2 single arm trial of palonosetron (PAL), a long acting 5-hydroxytryptamine (5-HT_3) receptor antagonist ($5HT_3$-RA), for the prevention of RINV in primary MG subjects receiving RT (54-60 Gy) and concomitant multi-dose, daily TMZ (75 mg/m^2) +/- bevacizumab. Results from this study demonstrate that a $5HT_3$-RA, such as PAL or ondansetron, can be safe and effective, however based on the results, there is still room for improvement of anti-emetic response related to CR rates and HRQoL, which could be addressed by combining a 5-HT_3-RA and NK_1-RA[12]. PAL was safe and effective; however, there is room for improvement in the CR rates and HRQoL, which may be achieved with rolapitant plus ondansetron, a potentially more effective combination anti-emetic regimen. Additionally, PAL is only available as an IV injection in the United States whereas ondansetron can be administered orally, making it a more patient-friendly drug. The most studied agents in the RINV settings are the $5HT_3$-RAs, with overall moderate response and low toxicity. However, agents such as the tachykinin NK-1 receptor antagonist may play a role in improving response rates, but there needs to be further studies in randomized controlled trials.[13]

The oral combination of rolapitant plus ondansetron has not been studied in the prevention of RINV using *multi-dose* chemotherapy especially in individuals with malignant glioma. Additional advantages to using rolapitant plus ondansetron in the setting of radiation with concurrent multi-dose oral chemotherapy are that it avoids side effects associated with intravenous administration (e.g. palonosetron) and eliminates treatment room costs. Furthermore, rolapitant, as opposed to the aprepitant or netupitant, is not a CYP3A4 inhibitor or inducer of for common drugs used in glioma patients (e.g. dexamethasone, enzyme-inducing anticonvulsants, or irinotecan) thus reducing drug-induced side effects. The NK_1 antagonist EMEND® (aprepitant) was approved by the US Food and Drug Administration and by the European Medicines Agency for the prevention of acute and delayed CINV associated with highly emetic chemotherapy (HEC- i.e. high dose cisplatin) and MEC when used in combination with a 5-HT_3 antagonist and a corticosteroid. Dosage adjustment of concomitantly administered drugs is necessary with aprepitant, which is a mixed inducer/inhibitor of cytochrome P450 (CYP) 3A4 and also affects other CYP enzymes. Rolapitant has been free of clinically relevant drug interactions in studies conducted to date, has rapid and good brain penetration which may contribute to its quick onset of action, and a long half-life that allows for dosing only once during each cycle of chemotherapy. Rolapitant has been selected as a promising agent to address this and other shortcomings of existing therapy. As described above, PET occupancy studies as well as clinical efficacy data support the use of only a single dose of rolapitant to protect patients from CINV. Efficacy or complete response be assessed during weeks 1-2. Complete response (CR) is defined as the proportion of patients without an emetic episode or use of rescue medication while receiving radiation and concomitant temozolomide).

Patient-centered care as it relates to patient preference and satisfaction has become one of the major goals in healthcare reform and transformation. Patient centeredness is a dimension of health care quality because of its connection with desired aims, like safety and effectiveness. Patient centeredness and satisfaction shifts the control from the hands of those who give care into the hands of those who receive it. Patient satisfaction with healthcare medications has been shown to affect treatment-related behaviors such has their likelihood of complying and continuing to use their medication correctly.[16]Thus, patient satisfaction translates into improved patient-centered outcomes and quality of care. The basis for this assessment will be overall patient medication satisfaction/preference at the end of week 3 and 6. More descriptive data (effectiveness, convenience and global satisfaction) relating to a patient's choice will be measured as a secondary outcome by the reliable and validated TSQM-9 tool.

Standard practice within the PRTBTC for prophylactically preventing nausea and vomiting associated with chemoradiation is the administration of ondansetron. With the administration of ondansetron orally 1 - 3

times a day for multiple days, compliance is a problem within this patient population. Newer approaches to treatment such as a single dose rolapitant should have fewer or minimal compliance problems. Hence, there is interest in understanding patient efficacy and preference relative to ondansetron. Compliance of ondansetron vs. rolapitant and ondansetron is also of interest.

Evidenced-based guidelines and clinical research recommend that future studies should consider the use of $5HT_3$-RAs and NK1=RA with current therapies and in other clinical settings, such as radiation therapy. Studies at the PRTBTC at Duke have evaluated intravenous palonosetron in RINV. However, rolapitant has not been studied in the prevention of RINV in malignant glioma. Rolapitant plus ondansetron in the setting of radiation with concurrent oral chemotherapy (e.g. temozolomide) is advantageous in avoiding intravenous administration side effects and treatment room costs. Furthermore, rolapitant and ondansetron as opposed to ondansetron monotherapy (up to three times a day for seven day/week) may ultimately increase compliance and decrease costs. The single dose rolapitant in combination with ondansetron may be beneficial to the brain tumor patient population for three specific reasons: (1) rolapitant may increase antiemetic efficacy and (2) compliance in patients with gliomas who often "forget" to take multiple oral dosed medications due to memory impairment (3) and may prevent toxicity (e.g. interaction with enzyme inducing anticonvulsants) that is associated with administration of other longer acting antiemetics (e.g. aprepitant). **Ultimately, rolapitant plus ondansetron may improve overall efficacy (CR rates), cost, HRQoL and patient satisfaction.**

8 OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Analysis
Primary	Compare the efficacy of rolapitant plus ondansetron vs. ondansetron monotherapy in the prevention of nausea and vomiting, as measured by the overall complete response (CR) rate, among malignant glioma patients during RT and concomitant TMZ	Complete response (CR) rate associated with rolapitant plus ondansetron and ondansetron alone during the first two weeks of RT and concomitant TMZ. The CR rate is defined as the proportion of patients with no emetic episode or use of rescue medication while receiving radiation and concomitant TMZ. The CR rate will be assessed via the modified MASCC Antiemesis Tool (MAT) within daily diary.[17] [18]	See section 15.4
KEY Secondary	Assess whether malignant glioma patients receiving RT and concomitant TMZ are more satisfied with rolapitant plus ondansetron vs. ondansetron monotherapy for the prevention of RINV	The percentage of patients who prefer rolapitant plus ondansetron over ondansetron alone, as determined by response to the question with "Which nausea medication regimen was I most satisfied with?"	See section 15.5.1
Secondary	Describe the rationale behind a patient's satisfaction with antiemetic preference based upon effectiveness, convenience & global satisfaction	Mean patient satisfaction scores during weeks 3 and 6 for effectiveness, convenience, and global satisfaction for ondansetron pill and rolapitant plus ondansetron using the 9-item TSQM-9 patient satisfaction survey.[16] Three subscales are computed: effectiveness (3 items), convenience (3 items), and global satisfaction (3 items).	See section 15.5.2
Secondary	Compare the efficacy of rolapitant plus ondansetron vs. ondansetron monotherapy in the prevention of nausea and vomiting separately, as measured by the respective CIN, CIV -CR rates, among malignant glioma patients during RT and concomitant TMZ	The CR outcomes for nausea will be defined in comparable terms (no use of rescue medication for nausea). The CR outcome for vomiting will be defined in comparable terms (no use of rescue medication for vomiting). The CIN, CIV CR rate will be assessed via the modified MASCC Antiemesis Tool (MAT) within daily diary.	See section 15.5.2
Secondary	Evaluate patient compliance with rolapitant plus ondansetron and ondansetron monotherapy	The compliance rate defined as the percentage of days that rolapitant plus ondansetron or ondansetron alone were used during the six weeks	See section 15.5.2
Secondary	Assess the safety of rolapitant plus ondansetron in the prevention of RINV in primary glioma patients receiving RT and concomitant TMZ	The percentage of patients experiencing a grade ≥3 treatment-related toxicity. Toxicity (adverse events) will be assessed throughout the 6-week treatment period. This data will be collected via NCI Common Toxicity Criteria (CTC) (vs 4)	See section 15.5.2

9 INVESTIGATIONAL PLAN

9.1 Study Design

This proposed single center study is a randomized phase II trial of rolapitant plus ondansetron vs. ondansetron monotherapy for the prevention of RINV in primary malignant glioma subjects receiving radiation therapy (RT) and concomitant multi-dose temozolomide (TMZ). All eligible subjects should receive a planned total dose of 54-60 Gy of radiation and 75 mg/m^2 of temozolomide daily for a total of six weeks. Glioma patients will be randomized in an unblinded fashion to receive one of two treatment sequences of antiemetic therapy for the prevention of nausea and vomiting associated with RT and concomitant TMZ.

Sequence A involves administration of ondansetron alone for 3 weeks followed by the use of rolapitant X 1 dose plus daily ondansetron for 3 weeks; whereas, sequence B involves the use of rolapitant X 1 dose plus daily ondansetron for 3 weeks followed by 3 weeks of daily ondansetron alone. For the rolapitant plus ondansetron weeks (1 or 4), patients will self-administer the oral rolapitant pills (180 mg dose) X 1 dose, 1-2 hours before the planned week of radiation fraction (see schema). Subjects will be given a prescription for ondansetron 8 mg pills to be taken 30 minutes before their TMZ dose. After the start of radiation therapy, the type of additional rescue antiemetic medication, if needed will be left up to the investigator's discretion, with what is in the best interest of the subject. Subjects will be educated that they are allowed to take rescue antiemetic medication in either arm. If the subject experiences nausea and vomiting and does take a rescue antiemetic, the subject will be asked to record the use of additional antiemetic in a medication log provided to them. Subjects will complete weekly medication logs and surveys (see appendices) to capture study outcomes. Subjects will be told that the study is voluntary and that they may exit at any time if they wish.

Approximately 170 patients will provide informed consent in order that 160 patients be randomized to either treatment sequence A or B. The 170 estimate is to allow for screen failures and dropout rates. All subjects must give written informed consent to participate in the study. Patients will be screened -28 - 0 days prior to the start of the study. During this time period the following information will be recorded: physical examination; vital signs and weight; laboratory studies (complete blood count with differential, blood chemistries, liver function tests and urinalysis): medical history; concomitant medications (steroids and anticonvulsants) and predictors of RINV (irradiation site, planned dose treatment field, alcohol intake, gender, age etc.). Laboratory evaluations, performance status, concomitant medications, and adverse events for final eligibility should be confirmed within 2 weeks of initiating radiation with concomitant TMZ . Patients will obtain standard of care blood work (per local oncologist) (complete blood count with differential, blood chemistries, liver function tests). Toxicity will be assessed based on the Common Toxicity Criterion (CTC version 4). The patient will be asked to complete the MASCC Antiemesis Tool (MAT- see appendices) nausea and vomiting questionnaire on day 0 (baseline) and days 1, 2, 4, and 7 of each week of radiation therapy. In addition, they will be asked to record their use of any antiemetic rescue medication.

At the end of weeks 3 & 6, the subject will be asked to fill out a Treatment Satisfaction Questionnaire for Medication (TSQM-9- see appendices) and will be asked at the end of week 6 to choose which antiemetic they prefer.

9.2 Standard of Care Chemotherapy Treatment Plan

Temozolomide is an oral alkylating agent which has demonstrated anti-tumor activity as a single agent in the treatment of recurrent glioma. As stated previously, Stupp et al (2005) have demonstrated an increase in efficacy of temozolomide in combination with radiation therapy in the adjuvant treatment of primary malignant gliomas. In addition, the regimen was considered safe. Non-hematological grade 2 toxicities included: Fatigue (26%), other constitutional symptoms (7%), rash and dermatologic side effects (9%), infection (1%), vision (14%), and nausea and vomiting (13%). Grade 3 / 4 non-hematological toxicities occurred <10%: Fatigue (7%), other constitutional symptoms (2%), rash and dermatologic side effects (1%), infection (3%), vision (1%), and nausea and vomiting with a $5HT_3$-RA (<1%). Thus, this safe and standard regimen will be utilized in this protocol. Daily temozolomide therapy will be calculated at a dose of 75 mg per square meter of

body surface area per day and be administered 7 days a week from the first until the last day of radiation therapy or a total of 42 days. Additional clinical and laboratory assessments will be at the discretion of the radiation therapist and oncologist.

9.3 Standard of Care Radiation Treatment Plan

As dictated by the Stupp (2005) regimen, radiation therapy will be administered as fractionated focal irradiation in daily fractions of 1.8-2 Gy given 5 days a week for ~ 6 weeks for a total of 54-60 Gy. Patients will be followed closely by a local radiation therapist throughout treatment. The radiation therapist and oncologist will conduct the standard physical exams and obtain the lab work necessary for the eligibility. Additional clinical and laboratory assessments will be at the discretion of the radiation therapist and oncologist.

9.3.1 Dose Definition and Schedule

The external beam radiation therapy (XRT) plan will be determined at the discretion of the local radiation therapist dependent on tumor size and location. It should begin 2-6 weeks after surgery. One treatment of 1.8-2.0 Gy will be given daily, 5 days per week, (30-33 fractions over less than seven weeks) for a total of 54-60 Gy. All portals shall be treated during each treatment session. Doses are prescribed at the maximum dose line encompassing $\geq$ 95% of the target volume.

9.3.2 Physical Factors

Treatment shall be delivered on megavoltage machines of energy ranging from 4 to 18 MV photons. Selection of the appropriate photon energy should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies > 10 MV should be utilized only in dual energy beam arrangements using at least one beam with energy < 10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm.

9.3.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or another appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays and provides adequate immobilization must be utilized at all times during planning and therapy to ensure reproducibility.

The initial target volume shall include the contrast-enhancing lesion and surrounding edema (if it exists) demonstrated on the pre-operative MRI plus a 2.0-cm margin. If no surrounding edema is present, the initial target volume should include the contrast-enhancing lesion plus a 2.5-cm margin. This primary target volume will be treated to 45-46 Gy in 23-25 daily fractions, at 1.8-2.0 Gy per fraction.

The boost volume will be based on the post-operative MRI performed during treatment planning. After 45-46 Gy, the boost volume will include the contrast-enhancing lesion plus a 1.5-cm margin or, if minimal contrast-enhancing lesion is present at a portion of the resection cavity on MRI, the surgical defect plus a 2.0-cm margin, whichever is greater at that segment of the MRI image. The boost volume will be treated to an additional 14-14.4 Gy in 7-8 daily fractions, 1.8-2.0 Gy per fraction. This will bring the total target dose to 54-60 Gy in 30-33 fractions. All parts of the target volumes are to receive at least 100% but no more than 110% of the dose at the prescription isodose line.

9.3.4 Treatment Planning and Safety

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple-field techniques, including intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT). MRI-guided 3D treatment planning is necessary to assure accuracy in the selection of field arrangements. Isodose distributions for the primary and boost target volume are required on all patients, including those treated with parallel-opposed fields. A composite plan is required showing the respective target volumes. The inhomogeneity across the target volume shall be kept to a minimum.

The maximum dose should be no higher than 112% of the prescription. Possible side effects include swelling of the brain, hair loss, localized skin irritation, low blood counts, fatigue, memory loss, hearing loss, nausea and/or vomiting, loss of appetite, headaches, radiation necrosis (death of tissue or skin), and secondary cancer.

9.3.5 Dose Limitations to Critical Structures

The lens and cervical spine must be shielded from the direct beam at all times. The maximum dose to the optic apparatus (optic chiasm, optic nerves, and eyes) must be limited to 54 Gy, and the brain stem limited to 60 Gy.

9.3.6 Safety Considerations

Safety will be assessed throughout the six weeks of radiation and 2 weeks post radiation using adverse event reporting by the clinical research nurse (CRN) using the Common Toxicity Criterion (CTC version 4.0). Monthly meetings conducted to review all adverse events and safety events with the PI, CRN, and CRC is standard of practice within the PRTBTC.

9.4 Anti-emetic Treatment

9.4.1 Antiemetic Treatment Plan

Sequence A involves administration of ondansetron alone for 3 weeks followed by the use of 1 dose of rolapitant plus daily doses of ondansetron for 3 weeks. Sequence B involves the use of 1 dose of rolapitant plus daily doses of ondansetron for 3 weeks followed by 3 weeks of ondansetron alone. For the rolapitant plus ondansetron weeks (1 or 4), patients will self-administer the single oral dose of rolapitant 1-2 hours before the first fraction of radiation on the planned week. Subjects will be given a prescription for ondansetron 8 mg pills to be taken 30 minutes before their daily TMZ dose. After the start of radiation therapy, the type of additional rescue antiemetic medication, if needed will be left up to the investigator's discretion. Subjects will be informed that they are allowed to take rescue antiemetic medication in either arm of the study. If the subject experiences nausea and vomiting and does take a rescue antiemetic, the subject will be asked to record the use of an additional antiemetic in the medication log provided to them. Subjects will complete weekly medication logs and surveys (see appendices) to capture study outcomes. Subjects will be told that the study is voluntary and that they may exit at any time if they wish.

9.4.2 Missed Doses

Patients will be reminded by the study team via a weekly phone call to take daily ondansetron and the rolapitant prior to weeks 1 or 4 of radiation depending on the assigned sequence (A vs. B). The time and date of ondansetron and rolapitant administration will be recorded in the patient medication log (see appendices). Subjects will be required to contact their treating physician for instructions if they forget to take rolapitant before the scheduled week of radiation or ondansetron before their daily chemotherapy. Rescue medication (e.g. ondansetron 8 mg p.o.) will be used to make up a missed dose.

9.4.3 Concomitant Medications

Prophylactic medication for the prevention of nausea and vomiting 24 hours prior to the start of radiation therapy through the full course of radiation therapy is prohibited, with the exception of the study drugs. Corticosteroids will be allowed for treatment of cerebral swelling. Rescue medication for treatment of nausea and vomiting is permitted while receiving radiation therapy at the discretion of the investigator. The date(s) of the rescue medication administration will be recorded in the patient medication log (see appendices).

9.5 Study Drug Blinding

Not applicable

9.6 Randomization

A permuted block randomization will be used to assign patients, in an unblinded fashion, to one of two treatment sequences as described in Section 9.1. A 1:1 allocation ratio will be used.

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

Rolapitant is an FDA-approved, novel long-acting new highly selective NK_1 receptor antagonist (RA) that is designed to be given in combination with a $5HT_3$-RA (i.e. ondansetron) to prevent CINV. Based on preclinical data and the half- life (170 hrs.) described previously and below, ***one oral*** rolapitant dose of 180 mg will be administered in combination with oral daily ondansetron at 8 mg/day to provided antiemetic coverage for 3 weeks of radiation (3-half-lives for rolapitant). Sequence A involves administration of ondansetron alone for 3 weeks followed by the use of rolapitant X 1 dose plus ondansetron for 3 weeks; whereas sequence B involves the use of rolapitant X 1 dose plus ondansetron for 3 weeks followed by 3 weeks of ondansetron alone. For the rolapitant plus ondansetron weeks (1 or 4), patients will self-administer the oral rolapitant pill 1-2 hours before the first fraction of radiation on the planned week (see schema). The rolapitant doses will be supplied by TerSera.

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

An evaluable subject is defined as a patient who meets eligibility criteria and completes at least two weeks of radiation for first CR and ~ 6 weeks of radiation for additional secondary outcomes.

9.9 Early Study Termination

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 12.6, which describes procedures and process for prematurely withdrawn patients.

10 STUDY DRUG

10.1 Names, Classification, and Mechanism of Action

Rolapitant or Varubi® (formerly referred to as SCH 619734) is an FDA-approved potent, selective, competitive neurokinin-1 (NK_1) receptor antagonist with no known activity at other pharmacologic targets. It binds with high affinity to the human NK_1 receptor (Ki = 0.66 nM) and competitively antagonizes functional effects mediated by activation of the NK_1 receptor in cultured cells (Kb = 0.45 nM). The endogenous activator of NK_1 receptors is the neuropeptide Substance P. Rolapitant does not have significant affinity for NK_2 or NK_3 receptors or for a battery of other receptors, transporters, enzymes, and ion channels. The compound is active in animal models of chemotherapy-induced nausea and vomiting (CINV) and has demonstrated efficacy in phase 2 studies in patients receiving highly emetogenic chemotherapy (HEC). Because NK_1 RA is known to be effective in CINV have also been shown to be effective in postoperative nausea and vomiting (PONV), rolapitant has also been investigated and shown to be effective in a phase 2 study in the prevention of PONV.

The first indication for which rolapitant is being developed is the prevention of CINV. CINV has both an acute (0 to 24 hrs.) and delayed (>24 to 120 hrs.) phase and it was expected that rolapitant will be very effective in preventing CINV both phases in patients receiving either HEC or MEC agents. Cisplatin doses $\geq$60 mg/m^2 represent the standard chemotherapy agent used in many clinical trials to determine effectiveness of anti-CINV therapies against a HEC regimen. MEC includes chemotherapy agents that are categorized as Hesketh 3 or 4 and include carboplatin, cisplatin (<50 mg/m^2) and cyclophosphamide regimens such as cyclophosphamide 750 – 1500 mg/m^2 IV alone or combined with other chemotherapy agents and

cyclophosphamide 500 – 750mg/m^2 administered with other emetogenic chemotherapy (Hesketh level 3, other than cyclophosphamide). MEC clinical trials often include breast cancer patients receiving a combination of intravenous cyclophosphamide plus an anthracycline drug such as doxorubicin or epirubicin. There are both acute (0 to 24 hrs.) and delayed (>24 to 120 hrs.) phases of CINV which are distinct after HEC but less differentiated after MEC.

10.2 Packaging and Labeling

The drug product will be supplied in blister packs containing two (2) 90 mg tablets provided by TerSera.

10.3 Supply, Receipt, and Storage

Study drug supplies must be stored in a secure, limited-access location under the storage conditions specified on the drug supply label. Rolapitant tablets are stored at controlled Room temperature, 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

10.4 Dispensing and Preparation

There is no preparation as each 90 mg pill is packaged in a separate sealed blister pack. The study pharmacist will dispense 2-90 mg pills (for a total dose of 180mg) to the patients to be administered either on week 1 or 4 depending on assigned sequence as directed by the study team.

10.5 Compliance and Accountability

Patients will be reminded by the study team to begin rolapitant during week 1 or 4 of radiation depending on assigned sequence. Patients will also be reminded to take daily ondansetron. Compliance will be recorded by study coordinator through weekly patient questioning and patient recording in medication log (see appendices). Of note compliance is a secondary objective (see Section 15.5).

10.6 Disposal and Destruction

The ICS will either destroy or return the unused study drug at the discretion of TerSera. The investigational pharmacist will be responsible for performing and documenting such activities.

10.7 Other Study Drugs (Ondansetron)

10.7.1 Description

Ondansetron is a first generation 5-HT_3-RA (serotonin-3).

10.7.2 Source

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

10.7.3 Dosage and Administration

Ondansetron will be administered on both arms of the protocol at 8 mg p.o, daily on Days 1- 42 days, 30-60 minutes prior to each dose of chemotherapy. A prescription for Ondansetron 8 mg p.o. daily 30-60 minutes before temozolomide X 7 days (with 6 refills) will be provided by provider.

10.7.4 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.

11 SUBJECT ELIGIBILITY

11.1 Inclusion Criteria

Selection of Subjects: Patients with a malignant glioma who plan to undergo standard RT with concomitant daily temozolomide (TMZ) therapy**.**

Please refer to section 5.4 for a complete listing of the Inclusion Criteria.

11.2 Exclusion Criteria

Please refer to section 5.4 for a complete listing of the Exclusion Criteria.

12 SCREENING AND ON-STUDY TESTS AND PROCEDURES

Patients will be initially screened during the -28 to 0 days prior to study initiation. During this time period, the following will be recorded: physical examination; vital signs and weight; laboratory studies (complete blood count with differential, platelet, blood chemistries, liver function tests and urinalysis); past medical history; concomitant medications (steroids and anticonvulsants); and predictors of RINV (e.g. irradiation site, planned dose, treatment field, alcohol intake, gender, age). Prior to study enrollment, patient's medications should be reviewed by the clinical pharmacist to prevent concerns with drug interactions. The patient's medications will be evaluated by the PI, the patient's study physician, and/or the study pharmacist on a case by case basis for safety. Laboratory evaluations, performance status, concomitant medications, and adverse events for final eligibility should be confirmed within 2 weeks of initiating radiation with concomitant TMZ.

Patients will be filling out data collection tools (i.e. MAT and TSMQ-9) day 0 (baseline) and days 1, 2, 4, and 7 (for days 7, 1, 2-3, and 4- 6, respectively) of each week of radiation therapy. In addition, they will be recording their medication and the use of rescue medication in a medication log as noted below (See Section 12.7 and appendices for study tools).

The CRC will be collecting data from the tools listed below and placing data in an electronic database that is 21CFR Part 11 compliant (e.g. Medidata Rave). Monthly meetings between the CRC and primary investigators will occur to review data. Patient Surveys and follow up phone calls will be conducted weekly to obtain and validate data. The CRC is required to monitor protocol patients weekly or as many times as necessary to obtain toxicities. Toxicities are 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 is to be used to score the adverse advents. All graded toxicities are then entered in the database and reviewed together with the Primary Investigator (PI) and CRC and confirmed by source documents. Attributions are approved by primary investigators.

Table 7: Screening and Study-related Tests and Procedures

Phase	Screen	Start	Study Period				End
Week of radiation	-4 to 0	1	2	3	4	5	6
Days of radiation	-28 to 0	1-7	8- 14	15-21	22-28	29-35	36-42
General Evaluations							
Informed Consent	X						
Eligibility Criteria	X[5]						
Past Medical History (RINV predictors)	X						
Physical Exam	X						
Height, Weight, BSA	X						
Vital Signs	X						
Performance Status	X[2]						
Concomitant Medications	X[2]	X					
Adverse Events	X[2]	Continuous[1]					
Laboratory Evaluations							
CBC with Platelets	X[2]						
Serum Chemistry tests	X[2]						
Liver Function tests	X[2]						
Serum Pregnancy Test	X[2]						
Urinalysis	X[2]						
Treatment							
Sequence A: Rolapitant (Day)					X(22)		
Sequence B: Rolapitant (Day)		X(1)					
Sequence A/B: Daily Ondansetron		X(1-7)	X (8-14)	X(15-21)	X(22-28)	X(29-35)	X(36-42)
Concomitant Temozolomide		X	X	X	X	X	X
Surveys/Medication log							
Medication Log		X	X	X	X	X	X
MAT Survey (Day 0 (baseline) and Days 1,2,4,7/week)[3]	X	X	X	X	X	X	X
TSQM9 Sequence A for wks1-3; 4-6					X(22)[4]		X(43)[4]
TSQM9 Sequence B for wks1-3; 4-6					X(22)[4]		X(43)[4]

1. Adverse events will be monitored until at least 30 days after the dose of Rolapitant (or 2 weeks after the end of radiation)
2. Laboratory evaluations, performance status, concomitant medications, and adverse events for final eligibility should be confirmed within 2 weeks of initiating radiation with concomitant TMZ.
3. MASCC questionnaire on Day 0 (baseline), and Days 1, 2, 4, and 7 (for days 7, 1, 2-3, 4-6, respectively)
4. TSMQ-9 administered after week 3 (Day 22) and after week 6 of radiation (Day 43)
5. Eligibility criteria should be checked after informed consent (-4 to 0 weeks) and should be confirmed within 2 weeks of initiating radiation and concomitant TMZ.

12.1 Screening Examination

The screening examination will take place between Day -28 and 0. Laboratory evaluations, performance status, concomitant medications, and adverse events will be confirmed within 2 weeks of initiating radiation and concomitant TMZ. An informed consent will be signed by the patient before any screening procedure takes place. Subject data to be collected at the Screening Examination as listed above in **Table 7** includes the following: physical examination; vital signs and weight; laboratory studies (complete blood count with differential, platelet, blood chemistries, liver function tests, urinalysis, and Beta-HG); past medical history; concomitant medications (steroids and anticonvulsants); and predictors of RINV (e.g. irradiation site, planned dose, treatment field, alcohol intake, gender, age).

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

12.2 Treatment Period

The treatment period will consist of six weeks of radiation and concomitant temozolomide as previously described above. Sequence A involves administration of ondansetron alone for 3 weeks followed by the use of

rolapitant X 1 dose plus daily ondansetron for 3 weeks; whereas, sequence B involves the use of rolapitant X 1 dose plus daily ondansetron for 3 weeks followed by 3 weeks of daily ondansetron alone. For the rolapitant plus ondansetron weeks (1 or 4), patients will self-administer the oral rolapitant pill 1-2 hours before the first radiation fraction on the planned week (see schema). Subjects will be given a prescription for ondansetron 8mg pills to be taken 30 minutes before their TMZ dose. After the start of radiation therapy, the type of additional rescue antiemetic medication, if needed, will be up to the investigator's discretion. Subjects will be informed that they are allowed to take rescue antiemetic medication in either arm. If the subject experiences nausea and vomiting and does take a rescue antiemetic, the subject will be asked to record the use of additional antiemetic in a medication log provided to them. Subjects will complete weekly medication logs and surveys (see appendices) to capture study outcomes. Subjects will be told that the study is voluntary and that they may exit at any time if they wish.

12.3 End of Treatment

The end of treatment will occur at the last day of radiation therapy and will include the weekly study assessments outlined above (see appendices).

12.4 Follow-up Period

The follow-up period will consist of a two-week period following chemoradiation treatment (or at least 30 days from the last dose of rolapitant in Sequence A) in order to identify and collect any additional toxicity during this time.

12.5 End of Study

The study will be considered complete once enrollment has been met, follow-up procedures on all subjects have been conducted, and data analysis is concluded. The study may also be terminated early for any reason by the PI-sponsor. In order to terminate the study with the Duke IRB, all data extraction and analysis must be complete. Therefore, if any articles for publication are derived from the current study, they must be submitted and accepted with no further need for additional data review prior to termination with the IRB.

Subjects that are lost to follow-up will be documented in the patient record and in the 21 CFR Part 11 compliant database (e.g. Medidata Rave). In the eCRF, the subject will be marked at "Patient Status Unknown," along with a corresponding explanation, if any. This status may also be documented on an "Off Study Form" in the eCRF.

12.6 Early Withdrawal of Subject(s)

12.6.1 Criteria for Early Withdrawal

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

- Adverse events or intolerable symptoms
- Abnormal laboratory values
- Abnormal test procedure results
- Protocol deviation
- Administrative issues
- Pregnancy
- Non-compliance of the subject

12.6.2 Follow-up Requirements for Early Withdrawal

Subjects who prematurely withdraw due to toxicity will be followed for two weeks after a subject is removed from the study. End of study requirements outlined above will be conducted.

12.6.3 Replacement of Early Withdrawal(s)

Not applicable

12.7 Study Assessments

12.7.1 Medical History

Standard medical history assessments will be conducted and recorded per institutional guidelines. Past medical history will include predictors of RINV (e.g. irradiation site, planned dose, treatment field, alcohol intake, gender, age etc.). The MAT survey will capture known patient reported predictors (see appendices).

12.7.2 Physical Exam

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

12.7.3 MASCC Antiemesis Tool (MAT)

The MAT is a validated, reliable and easy-to-use clinical tool consisting of an eight-item assessment of acute and delayed CINVCR rates.[18] It was developed by the Multinational Association of Supportive Care in Cancer (MASCC) members to assist patients and oncology professionals in communicating accurately about the prevention and control of nausea and vomiting that may occur with chemotherapy. The concept of the MAT is to provide an easy-to-use and easy-to-evaluate tool to assist in providing the best individual care to patients. Additionally, the tool was designed to aid treatment centers in understanding the effectiveness of their antiemetic strategies. The internal consistency reliability of the scale was high, with Cronbach alphas of 0.77 (patient sample) and 0.82 (care-giver sample). Responses were similar between the UK and U.S. samples in terms of nausea and vomiting, and both samples found the scale easy to use. Contrasted-groups validity (using age as a grouping variable) and concurrent validity (MAT compared with Rhodes Index for nausea, vomiting and retching -INVR) suggested that the scale is sensitive to detect the different dimensions of CINV and performed well against a daily assessment of nausea/vomiting (total score correlation r=0.86, P<0.001). Recall of events was high even three weeks after chemotherapy (correlations with INVR of 0.44-0.99, all P<0.01). Factor analysis clearly identified three factors, namely vomiting, acute nausea, and delayed nausea. Proxy assessments by caregivers were congruent with the patients' responses, especially in relation to vomiting. The MAT facilitates discussion between clinicians and patients about their nausea and vomiting experience, thereby potentially aiding treatment decisions. Assessments of CINV CR rates are conducted at baseline and weekly on days 1, 2, 4 and 7, and ultimately will capture data for all days a patient is in the study (See Section 12 and appendices).

12.7.4 Treatment Satisfaction Questionnaire for Medication (TSMQ-9)

To evaluate patient preference for the combination of rolapitant plus ondansetron vs. ondansetron alone, the patients will fill out the valid TSMQ-9 questionnaire for weeks 1-3 and weeks 4-6 (see schema). Analysis of the patient satisfaction or preference endpoint can be found in Section 15.5.2.

The 14-item Treatment Satisfaction Questionnaire for Medication (TSQM) Version 1.4 is a reliable and valid instrument to assess patients' satisfaction with medication, providing scores on four scales – side effects, effectiveness, convenience and global satisfaction.[16] In naturalistic studies, administering the TSQM with the side effects domain was thought to provoke the physician to assess the presence or absence of adverse events in a way that is clinically atypical, carrying the potential to interfere with routine medical care. As a result, an abbreviated 9-item TSQM (TSQM-9), derived from the TSQM Version 1.4 but without the five items of the side effects domain was created.[16] In a study using an interactive voice response system (IVRS)-administered TSQM-9, it was psychometrically evaluated

among patients taking antihypertensive medication. TSQM-9 domains had high internal consistency as evident from Cronbach's alpha values of 0.84 and greater.[16] TSQM-9 domains also demonstrated good test-retest reliability with high intraclass correlation coefficients exceeding 0.70.[16] As expected, the TSQM-9 domains were able to differentiate between individuals who were low, medium and high compliers of medication, with moderate to high effect sizes.[16] There was evidence of convergent validity with significant correlations with the medication adherence scale.[16] The TSQM-9 was found to be a reliable, valid tool to assess treatment satisfaction in naturalistic study designs, in which there is potential that the administration of the side effects domain of the TSQM would interfere with routine clinical care.

13 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

13.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition and the onset of new illness. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of rolapitant plus ondansetron vs ondansetron alone whether or not related to use of the rolapitant plus ondansetron vs ondansetron alone. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

From the time the subject signs the informed consent form through the End of Study visit (as defined in Section 12.5), all AEs must be recorded in the subject medical record and adverse events case report form.

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

Attribution of AEs will be indicated as follows:

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

13.1.1 Reporting of AEs

Not required by sponsor

13.2 Serious Adverse Events

An AE is considered “serious” if, in the opinion of the investigator, it is one of the following outcomes*:

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

*Exception: Preplanned (at time of informed consent) hospitalization for elective procedures, for protocol compliance or social reasons, or for observation will not be considered criteria for an SAE. The reason for the planned hospitalization should be documented. Complications experienced during these hospitalizations must be reported as SAEs if hospitalization is prolonged due to AE, or if the complication meets other serious criteria.

13.2.1 Reporting of SAEs

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

13.2.1.1 Reporting to TerSera

Serious adverse events that the Duke Sponsor-Investigator determines to be serious and related to rolapitant is to be shared with TerSera via MedWatch or CIOMS I form within 3 working days of Investigator awareness. If supporting documentation is included in the submission to TerSera (e.g., hospital reports, consultant reports, death certificates, autopsy reports, etc.), please redact any patient identifiers (including Medical Record number).

TerSera SAE Contact Details

- Email: TESAROPV@UBC.com
- Fax: 1.866.750.6823

13.2.2 Reporting Product Complaints for TerSera Products

Any written, electronic or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the Sponsor Institution or qualified designee to TerSera Call Center (US Call center: TerSera@medinfodept.com) within 1 working day of first becoming aware of the possible defect. This report to TerSera may also be made by telephone to the designated TerSera representative (1-844-483-7276) or by fax to the Call Center (1-913-451-6409). The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

13.3 Special Warnings and Precautions

Not Applicable

13.4 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews include, but may not be limited

to, review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 14.1 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk 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.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. 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.

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 Cancer Protocol Committee, the Safety Oversight Committee (SOC), the sponsor, 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.

14.2 Audits

The Duke Office of Audit, Risk and Compliance (OARC) office may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the OARC auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the OARC auditor(s) in order to discuss findings and any relevant issues.

OARC audits are designed to protect the rights and well-being of human research subjects. OARCA 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 1 studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

OARC 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.

14.3 Data Management and Processing

14.3.1 Case Report Forms (CRFs)

The electronic CRF will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only approved study staff (the PI, the research coordinators, the research nurses, the data management team, and the clinical trials manager), are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system, which will be a 21 CFR Part 11 compliant database (e.g. Medidata Rave). Designated personnel will complete user training, as required or appropriate per regulations.

14.3.2 Data Management Procedures and Data Verification

Designated personnel (e.g. the data management team and the clinical trials manager) using the electronic CRF will have access based on their specific roles in the protocol.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the data management team and the statistical team will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

14.3.3 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:
- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

15 STATISTICAL METHODS AND DATA ANALYSIS

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

15.1 Analysis Sets

The analysis of the complete response endpoint will focus on all patients randomized to sequence A or B. However, the analysis of the patient preference endpoint will focus on those patients who have experienced both regimens and provided a preference assessment. Safety analyses will include all patients who receive protocol treatment.

15.2 Patient Demographics and Other Baseline Characteristics

The socio-demographic and clinical characteristics of all randomized patients will be summarized by sequence assignment using means/SD, medians, percentiles, frequencies/proportions.

15.3 Treatments

Within each sequence assignment, a frequency distribution will be generated for the number of weeks of anti-emetic therapy received when ondansetron was administered alone, and when ondansetron was administered with rolapitant.

15.4 Primary Objective

The primary objective of this study is to compare the efficacy of rolapitant plus ondansetron vs. ondansetron alone in the prevention of nausea and vomiting, as measured by the overall complete response rate, among malignant glioma patients during RT and concomitant TMZ (see Section 8).

As described in Sections 15.6 and 15.7, the study was originally designed to enroll 170 glioma patients with the expectation that 160 patients would be randomized to receive one of two treatment sequences of anti-emetic therapy for the prevention of nausea and vomiting associated with RT and concomitant TMZ. A formal interim analysis was planned after 80 patients had been randomized (i.e. 40 patients to each treatment sequence). As of mid-January 2022, 53 patients had been randomized. On January 18, 2022, TerSera, the study's funding source, requested that accrual to the study be terminated in the next few months.

Given this request from TerSera, the accrual target for this study is reduced to 57 patients. The decision to terminate early has not been influenced by the data collected to date, as no interim analyses have been conducted. The analyses as described below will be conducted; however, they may no longer have the power to detect the hypothesized effect size.

15.4.1 Variable

Complete response (CR) rate associated with rolapitant plus ondansetron and that associated with ondansetron during the first two weeks of RT and concomitant TMZ is defined as the proportion of patients with no emetic episode or use of rescue medication while receiving radiation and concomitant TMZ. The CR rate will be assessed via the modified MASCC Antiemesis Tool (MAT).[17]

15.4.2 Statistical Hypothesis, Model, and Method of Analysis

As the primary analysis, a chi-square test will compare treatment regimens (ondansetron alone vs rolapitant + ondansetron) with respect to the proportion of patients who experience a CR during the first 2 weeks of RT and TMZ treatment. As an additional analysis, logistic regression will assess the effect of potential confounders on this relationship. Among the covariates that will be considered is the dose of decadron administered during the 2 weeks of RT and TMZ treatment.

As an exploratory analysis, a generalized linear model with a logit link that accounts for correlation between the CR status observed during the first and second treatment period within the same patient will be used to assess the impact of period, treatment, and their interaction. The purpose of this latter analysis is to assess whether the incremental effect of combination treatment relative to ondansetron alone is the same whether rolapitant is administered during the first period (i.e. first 3 weeks) or the second period (i.e. the second 3-week treatment regimen). It should be noted that this test will have low power to detect a clinically meaningful interaction effect. Within the context of the generalized linear model described above, the impact of covariates on CR rate will be explored. Included among these covariates will be the dose of decadron administer during that segment of the treatment regimen.

15.5 Secondary Objectives

Please refer to Section 8 for the secondary objectives and endpoints. The key secondary objective is to assess whether malignant glioma patients receiving RT and concomitant TMZ are more satisfied with rolapitant plus ondansetron vs. ondansetron for the prevention of RINV. Other secondary objectives include: (1) To describe

the rationale behind a patient's satisfaction with antiemetic preference based upon effectiveness, convenience, and global satisfaction, (2) To evaluate patient compliance with rolapitant plus ondansetron and ondansetron alone, and (3) To assess the safety of rolapitant plus ondansetron in the prevention of RINV in primary glioma patients receiving RT and concomitant TMZ.

15.5.1 Key Secondary Objective

The percentage of patients who prefer rolapitant plus ondansetron over ondansetron, as determined by response to the question with "Which nausea medication regimen was I most satisfied with?" will be calculated, with a 95% confidence interval. An exact binomial test assessing whether the proportion preferring the treatment regimen that includes rolapitant is 0.5 will be conducted. Logistic regression will explore the potential that sequence influences patient preference.

15.5.2 Other Secondary Objectives

Mean patient satisfaction scores for effectiveness, convenience and global satisfaction, will be computed based upon responses to the TSQM-9 treatment satisfaction survey[16] that patients complete at the end of week 3 after treatment with ondansetron alone or combination treatment. Three subscales will be computed: effectiveness (3 items), convenience (3 items), and global satisfaction (3 items). Assuming there is no evidence of a carry-over effect, a paired t-test will be conducted comparing satisfaction with combination treatment and with ondansetron treatment alone.

The efficacy of rolapitant plus ondansetron vs. ondansetron monotherapy in the prevention of nausea and vomiting will be separately assessed, as measured by the respective CIN, CIV CR rates, among malignant glioma patients during RT and concomitant TMZ. The CR outcome for nausea will be defined as no use of rescue medication for nausea, while the CR outcome for vomiting will be defined as no use of rescue medication for vomiting. The CIN and CIV CR rates will be assessed via the modified MASCC Antiemesis Tool (MAT).

For each 3-week treatment regimen, compliance is defined as the percentage of days that pills were appropriately used. The distribution of compliance during treatment with ondansetron alone and with combination treatment will be described with a frequency distribution. A nonparametric paired test (e.g. Wilcoxon) may be used to compare compliance within the two regimens (as documented on the medication logs).

For the manuscript, adverse events that are possibly, probably, and definitely treatment related that are reported during the ~ 6 weeks of treatment will be summarized. For each type of adverse event experienced by a patient during rolapitant plus ondansetron and during ondansetron treatment, the maximum grade experienced by each patient will be tabulated by treatment group (i.e. rolapitant plus ondansetron or ondansetron treatment). Given the cross-over design of this study, patients will contribute data to both treatment groups. Two tabulations of toxicity data will be generated for review by the Safety Oversight Committee including one that includes all toxicities regardless of attribution, and another that includes only toxicities that are possibly, probably, and definitely related to protocol treatment. For each of these tabulations, the maximum grade of each type of toxicity experienced by each patient will be summarized with frequency distributions within each treatment (rolapitant plus ondansetron vs. ondansetron). For ClinicalTrials.gov, serious adverse events and other adverse events will be summarized separately. These tabulations will reflect the number of patients who experience each type of toxicity regardless of grade or attribution.

15.6 Interim Analysis

Original Study Design: An interim efficacy analysis will be conducted after 40 patients are randomized to each sequence (a total of 80 patients). Given that the interim analysis will primarily focus on the complete response endpoint, study accrual will be suspended for approximately 2 weeks while the initial outcome data from all patients is collected. This interim analysis will allow early accrual termination for efficacy or for futility.

The O'Brien-Fleming analogue will define the alpha and beta spending function. The group sequential procedure for proportions within PASS has been used to simulate the following boundaries for comparing the CR rate in the two groups using a large-sample Z-test.[19,20]

	Significance Boundary		Futility Boundary	
Look	Z-Value Scale	P-value Scale	Z-Value Scale	P-Value Scale
1 (after 80 patients)	2.505	0.006	0.325	0.373
2 (after 160 patients)	1.657	0.049	1.657	0.049

At the time of the interim analysis, the combination would be considered superior to ondansetron monotherapy if the p-value was less than 0.006 and accrual terminated. If, on the other hand, the p-value associated with this comparison was 0.373 or larger, there would be a recommendation that accrual be terminated early due to futility.

These boundaries will be used as guidance in determining whether patient accrual should be terminated early. Other issues may also factor into that decision-making.

Modified Study Design: With the reduction in the study's accrual target as described in Section 15.4, no interim analyses are planned.

15.7 Sample Size Calculation

15.7.1 Original Study Design

One hundred seventy (170) glioma patients will be enrolled with the expectation that 160 patients will be randomized to receive one of two treatment sequences of anti-emetic therapy for the prevention of nausea and vomiting associated with RT and concomitant TMZ. A permutated block randomization with an allocation ratio of 1:1 will be used to assign patients to sequence A or B. Sequence A involves a 3-week regimen of daily ondansetron followed by a 3-week regimen consisting of rolapitant (day 22 only) and daily ondansetron; whereas Sequence B involves a 3-week regimen of rolapitant (day 1 only) and daily ondansetron followed by a 3-week regimen of daily ondansetron. The study has one primary and one KEY secondary endpoint: CR rate and patient overall preference for ondansetron treatment with or without rolapitant. Though the primary CR rate endpoint will focus on treatment during the first 2 weeks of RT and TMZ, a cross-over design is proposed so that a patient will experience both modes of treatment, and be equipped to make a comparative assessment of preference.

Power Calculations for Complete Response, Primary Endpoint: The power of the comparison of ondansetron and the combination of ondansetron and rolapitant relative to the CR rate during the initial 2 weeks of treatment with RT and TMZ will be considered here. This comparison will focus on the anti-emetic experience during the first regimen of the two treatment regimens that the patient will receive. Let

p_1 = overall complete response rate for the first 2 weeks of treatment with the combination antiemetic regimen, and

p_0 = overall complete response rate during the first 2 weeks of treatment with ondansetron alone.

The hypothesis that will be assessed is whether the CR rate with combination treatment is greater than that with ondansetron alone. Specifically, the hypothesis that will be tested is as follows:

$$H_0: p_1 \leq p_0 \text{ versus } H1: p_1 > p_0$$

Temozolomide prescribing information reports a vomiting rate of 20% with concomitant RT + TMZ. Anti-emetic treatment failure includes the occurrence of vomiting or the use of an anti-emetic for nausea and/or vomiting. Therefore, we anticipate that approximately 25% of patients receiving ondansetron alone to either vomit or receive an anti-emetic. Equivalently, a CR rate of 75% is anticipated with ondansetron alone.

One hundred sixty (160) patients will be randomized to either sequence A or B with the expectation that 152 patients will provide an assessment of their experience during the first 2 weeks of treatment with the first regimen. With 152 patients, there is 80% power to detect an increase in the CR rate from 75% with ondansetron to 90% with the combination of ondansetron and rolapitant (α=0.05; one-tailed).

Power Calculations for Patient Preference, KEY Secondary Endpoint: The hypothesis of this study is that patients will prefer the combination of ondansetron and rolapitant over ondansetron alone for the prevention of nausea and vomiting. If no overall preference exists, then the percentage of patients who choose combination treatment is expected to be approximately 50%. The hypothesis that will be tested is whether the proportion of patients who prefer combination treatment is greater than 50%. Statistically, the hypothesis that will be tested is:

$$H0: p \leq 0.5 \text{ vs } H1: p > 0.5$$

where p is the proportion of patients who prefer combination treatment over ondansetron alone. Under the assumption that approximately 140 patients will have experienced both regimens and provided a preference assessment, the study has 93% power to detect a preference rate of 65% or greater with a two-tailed test conducted at the 0.05 level of significance.

15.7.2 Modified Study Design

As described in Section 15.4, the sample size goal for this study is reduced to 57 patients. With 57 patients, there is 80% power to detect an increase in the CR rate from 75% with ondansetron to 97% with the combination of ondansetron and rolapitant (α=0.05; one-tailed). Alternatively, there is 80% power to detect an increase in CR rate from 63% to 90%.

Relative to patient preference, with 57 patients, the study has 83% power to detect a preference rate of 69% or greater with a two-tailed test conducted at the 0.05 level of significance.

16 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

16.1 Regulatory and Ethical Compliance

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

16.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

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

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

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

16.3 Informed Consent

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

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

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

16.4 Study Documentation

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, and CAP and CLIA laboratory certifications.

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

16.5 Privacy, Confidentiality, and Data Storage

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

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

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated 21 CFR Part 11 compliant database (e.g. Medidata Rave), which is housed in an encrypted and password-protected secure network drive. Access to electronic databases (without edit rights) will be limited to the PI, the study coordinator, and the statistical team. The only personnel with both access and edit rights to the electronic databases are the data management team, including the clinical trials manager. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

16.6 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Section 13.5 and 14.1.

16.7 Protocol Amendments

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

Though not yet required, the CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.).

16.8 Records Retention

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

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

17 REFERENCES

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18 APPENDICES

18.1 Appendix 1: Sequence A-TSQM9/MAT Questionnaire

Please see attached

18.2 Appendix 2: Sequence B-TSQM9/MAT Questionnaire

Please see attached

18.3 Appendix 3: Medication Log: Sequence A

Please see attached

18.4 Appendix 4: Medication Log: Sequence B

Please see attached

18.5 Appendix 5: Birth Control Recommendations

Please see attached