Olanzapine for the Treatment of Chronic Nausea and/or Vomiting in Advanced Cancer Patients

Study Protocol & Statistical Analysis Plan

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Title Page

OLANZAPINE FOR THE TREATMENT OF CHRONIC NAUSEA AND/OR VOMITING, UNRELATED TO CHEMOTHERAPY OR RADIATION, IN ADVANCED CANCER PATIENTS – A PILOT, DOSE-FINDING TRIAL.

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Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair or Co-Investigator
Questions related to data submission, or patient follow-up:	Study Chair or Co-Investigator
Questions regarding the protocol document:	Study Chair or Co-Investigator
Questions related to IRB issues and consent revisions:	Study Chair or Co-Investigator
Questions regarding CTEP-AERS reporting:	Study Chair or Co-Investigator

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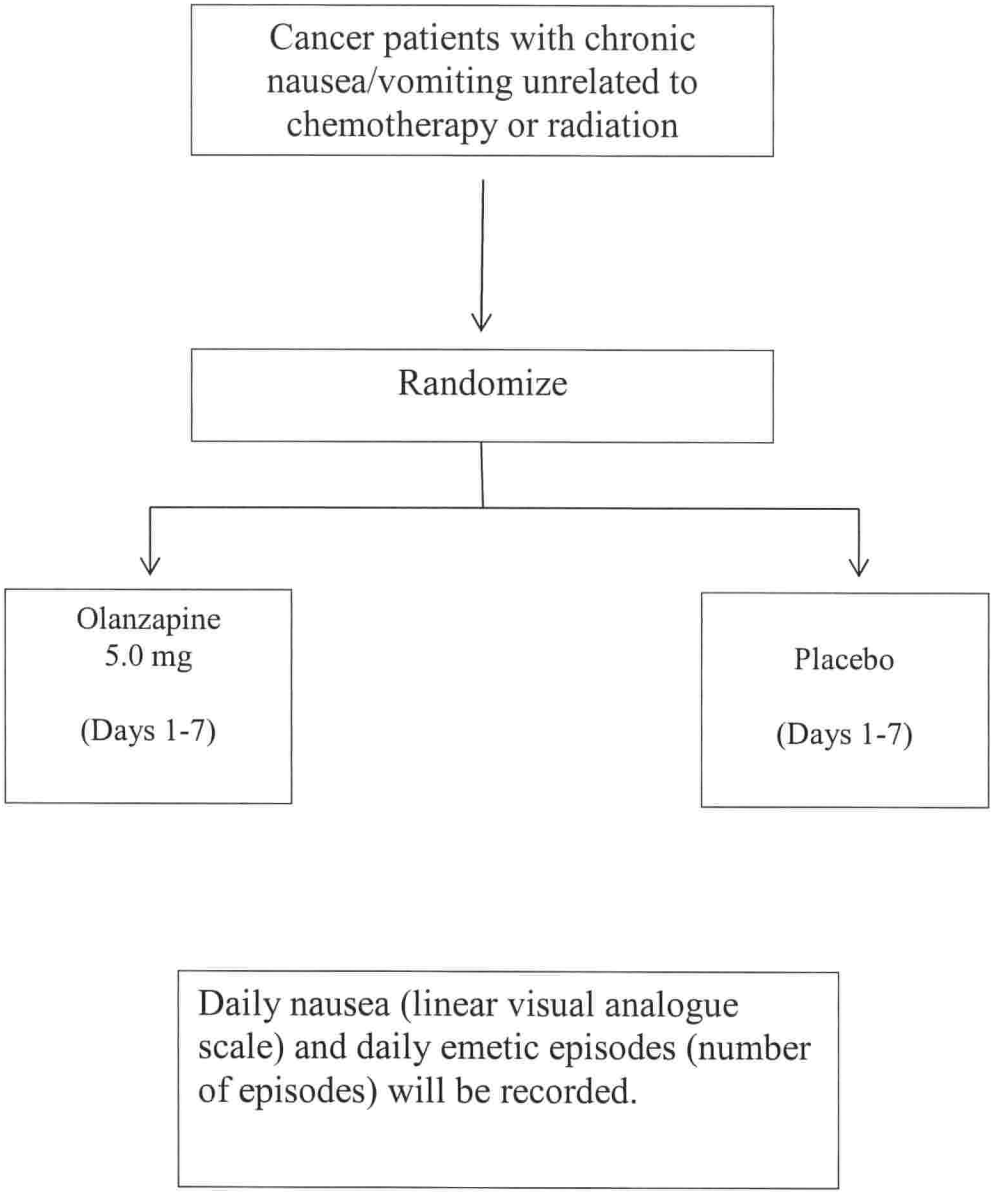
I. Schema


Cancer patients with chronic nausea/vomiting unrelated to chemotherapy or radiation
Randomize
Olanzapine 5.0 mg
(Days 1-7)
Placebo
(Days 1-7)
Daily nausea (linear visual analogue scale) and daily emetic episodes (number of episodes) will be recorded.

II. Background

Patients with advanced cancer experience multiple physical and psychosocial symptoms, including pain, fatigue, weight loss, lack of appetite, nausea, emesis, anxiety, dyspnea, and confusion (1-3). The causes of these symptoms can be related to the neoplasm and complications of treatments such as surgery, chemotherapy and/or radiation; the symptoms significantly affect the patients' quality of life (4). The particularly distressing symptom of chronic nausea may be present in over 60% of patients with advanced cancer (5).

Nausea is a subjective, difficult-to-describe, sick or queasy sensation, usually perceived as being in the stomach; it is sometimes followed by emesis (6). The experience of nausea is difficult to describe in individual people because it is a subjective sensation. Nausea has been assumed to be the conscious awareness of unusual sensations in the "vomiting center" of the brainstem, but the existence of such a center and its relationship to nausea remain controversial (6). Nausea and emesis are not always directly associated with each other. One can experience nausea without emesis and one can have sudden emesis without nausea.

The etiology of chronic nausea in advanced cancer patients is multifactorial. Etiologies include medications such as opioids, delayed gastric emptying, mechanical bowel obstruction, increased intracranial pressure, vestibular dysfunction, metabolic issues, and/or cortical effects such as anxiety or depression (2). Delayed gastric emptying and partial bowel obstruction may account for a significant cause of chronic nausea (2,7). Chronic nausea may persist for a significant time and cause complications such as anorexia and fatigue, impaired performance status, and diminished quality of life (2).

A number of palliative care studies have considered various empirical treatments of chronic nausea with limited success (8). One palliative care group has recommended metoclopramide and haloperidol for use as initial treatment for nausea and vomiting in advanced cancer, with olanzapine as second line therapy, and ondansetron as third line therapy (9). However, in 2013, the European Medicines Agency's Committee on Medical Products for Human Use recommended that the use of metoclopramide be limited due to serious neurological side effects (10).

Davis et al. (11) have reported a systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation. Ninety-three articles were found with fourteen of them being randomized clinical trials, most of low quality. Metoclopramide was felt to have had modest evidence for efficacy, but there was no evidence that multiple antiemetics or any specific antiemetic had significant efficacy based on the current data in the literature. The conclusion of the review was that antiemetic recommendations for chronic nausea in cancer patients are based on weak to moderate evidence at best, and prospective randomized trials of single antiemetics are needed to properly establish evidence-based guidelines.

Further evidence that new agents are needed to treat chronic nausea in cancer patients came from a recent trial demonstrating that dexamethasone was not superior to placebo in the management of chronic nausea in patients with advanced cancer in whom metoclopramide was not effective (12).

Based on these data and on a recent phase III study of the efficacy of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) (13), olanzapine appears to be a very reasonable candidate for study for the treatment of chronic nausea in patients with cancer. Olanzapine, an atypical antipsychotic agent of the thiobenzodiazepine class, was approved by the FDA for the treatment of the manifestations of psychotic disorders in 1996 (14,15) with a generic formulation becoming available in 2011. This drug blocks multiple neurotransmitter receptors including dopaminergic (D_1, D_2, D_3, D_4 brain receptors), serotonergic (5-HT_{2a}, 5-HT_{2c}, 5-HT_3, 5-HT_6 receptors), catecholaminergic (alpha$_1$ adrenergic receptors), acetylcholinergic (muscarinic receptors), and histaminergic (H_1 receptors) (16). Olanzapine has five times the affinity for 5-HT_2 receptors than for D_2 receptors (17). The effect of olanzapine on the serotonin-mediated 5-HT_{2C} receptor as well as other dopamine and serotonin receptors may explain, in part, its efficacy in alleviating nausea and vomiting.

A benefit of olanzapine is that it is not a cytochrome P450 inhibitor and thus appears to have fewer drug interactions than many other drugs (16). Common side effects are sedation and weight gain (18,19), and the weight gain can lead to diabetes mellitus when given for a period of greater than six months (20).

There have been case reports on the use of olanzapine as an anti-nausea agent for oncology conditions other than CINV (21-27). A patient with leukemia reported a significant improvement in chronic nausea with the use of olanzapine (25) and, in six patients receiving palliative care, olanzapine was reported to be effective for intractable nausea due to opioids, neoplasm, and/or medications (21). In another report, olanzapine was effective in controlling refractory nausea and vomiting in two patients with advanced cancer (26). Olanzapine was also reported to be effective in controlling opioid-induced nausea (27).

Bowel obstruction is one of the most common complications in patients with advanced cancer either due to the ingestion of pain medications, large or small intestinal dysfunction, or other tumor-induced issues (2,5). A retrospective study, carried out on a palliative care unit, demonstrated that, in 18 of 20 patients with incomplete bowel obstruction, the use of olanzapine led to a significant decrease in the average intensity score of nausea, suggesting a role for olanzapine in the symptom relief in patients with incomplete bowel obstruction (28).

The National Cancer Institute recently approved a multi-institutional phase III clinical trial (Alliance A221301) for the prevention of CINV in patients receiving highly emetogenic chemotherapy using olanzapine plus standard antiemetics compared to placebo plus standard antiemetics (29). The trial was based on substantial evidence that this drug is helpful for preventing chemotherapy-induced nausea and vomiting (30-34) and for treating nausea/vomiting that had occurred as a result of chemotherapy (13). This randomized, double-blind, phase III trial was performed in chemotherapy naïve patients receiving cisplatin, $\geq$70 mg/m^2, or cyclophosphamide-anthracycline-based chemotherapy, comparing olanzapine (OLN) to placebo (PLA) in combination with aprepitant (APR), a 5-HT$_3$ receptor antagonist (5-HT$_3$), and dexamethasone (DEX). The OLN regimen was 10 mg of oral OLN, 125 mg oral APR, a 5-HT$_3$, and oral DEX 12 mg pre-chemotherapy, day 1, and 10 mg/day of oral OLN on days 2-4 post-chemotherapy, 80 mg oral APR, days 2,3 post chemotherapy, and 8 mg oral DEX , days 2-4 post chemotherapy. The PLA regimen was oral placebo, day 1, and oral placebo on days 2-4 post chemotherapy, with the APR, 5-HT$_3$, and DEX pre and post-chemotherapy being the same as in the OLN regimen. Fosaprepitant (150 mg IV), day 1 could be substituted for the oral aprepitant. Palonosetron, ondansetron, or granisetron were the permitted 5-HT$_3$ options. Nausea was measured on a 0-10 visual analogue scale, with 0 being no nausea at all and 10 being nausea as bad as it can be.

Four hundred one patients were enrolled with 380 patients evaluable (192 patients receiving the OLN regimen and 188 patients receiving the PLA regimen). The proportion of patients with no nausea was significantly improved for the OLN regimen compared to the PLA regimen for the acute period (24h post-chemotherapy) (74% vs. 45%, p=0.002), for the delayed period (25 to 120 hours post-chemotherapy) (42% vs. 25%, p=0.002), and for the overall period (0-120 h) (37% vs. 22%, p=0.002). Complete response (CR) (no emesis, no rescue medications) was significantly improved in OLN compared to PLA patients for the acute (86% vs. 65%, p<0.001), the delayed (67% vs. 52%, p=0.007), and the overall periods (64% vs. 41%, p<0.001). There were no Grade 3 or 4 toxicities. No nausea, the primary endpoint, and complete response, a secondary endpoint, were significantly improved with OLN compared to PLA (29).

Based on the above, it appears that olanzapine has significant potential for use in the prevention and treatment of nausea in a palliative care setting including in patients with opioid-induced nausea. Due to its mechanism of action, blocking multiple neurotransmitter receptors, it can be used as a single agent; due to its long half-life, it can be given as once-daily dosing. Therefore, patient compliance should be reasonable.

The purpose of the current proposed study is to evaluate the use of olanzapine for the treatment of cancer patients with chronic nausea and/or emesis unrelated to chemotherapy or radiation in a randomized placebo-controlled pilot clinical trial.

Much thought was given to the appropriate control arm for this study. While we considered choosing a single comparator (such as haloperidol or metoclopramide), there was no established agent to recommend and patients may have already tried one that we might have chosen as a single comparator. There have been multiple recent treatment trials that have used physician's choice as a control, with good accrual and good results (35-37) and we considered this option. This topic regarding a control arm was

discussed in detail with community and academic investigators at various Alliance committees and meetings. In the end, it was decided to use a placebo arm in the study since nausea can be subjective and vary under multiple conditions and with different patients. If a patient has persistent nausea or vomiting 2-3 days after study enrollment, then they can opt out of the study, while still blinded to the treatment arm. This will allow this to be a treatment outcome of interest (with the hypothesis that more placebo patients will drop out than active treatment patients).

III. Study Objectives

Primary: To conduct a pilot trial to estimate the proportion of cancer patients with an improvement in chronic nausea, unrelated to chemotherapy or radiation after treatment, with olanzapine versus a placebo.

Secondary:

- To evaluate toxicity associated with olanzapine in the current situation
- To evaluate the number of patients in each study arm who stop therapy prior to 5 days
- To evaluate the utility of this trial design, including the defined patient eligibility, for potential use in a phase III trial, assuming that these data are promising from the current trial

IV. Study Plan

Patient Selection

Eligibility Criteria

Eligible patients will:

- Be at least 18 years of age,
- Have histologically or cytologically-confirmed malignant disease in an advanced incurable stage
- Have not received chemotherapy or radiation for ≥14 days (advanced cancer patients receiving hormonal therapy or targeted therapy that does not come with a recommendation for prophylactic anti-emetic therapy are eligible)
- Have chronic nausea that has been present for at least one week (worst daily score ≥3, 0-10 visual analogue scale) or vomiting at least five times over past one week
- Have serum creatinine ≤ 2.0 mg/dl and SGOT or SGPT ≤ 3 times upper limits of normal ≤120 days prior to registration.
- ANC ≥ 1500 mm3 <120 days prior to registration
- Not be receiving treatment with another antipsychotic agent such as risperidone, quetiapine, clozapine, phenothiazine or butyrophenone for ≤30 days prior to registration or planned during protocol therapy (patients may have received prochloperazine and other phenothiazines as prior anti-emetic therapy)
- Not have: concurrent use of ethyol; severe cognitive compromise; known history of CNS disease (e.g. brain metastases, seizure disorder); concurrent use of amifostine, concurrent abdominal radiotherapy; concurrent use of quinolone antibiotic therapy; chronic alcoholism (as determined by the investigator); known hypersensitivity to olanzapine; known cardiac arrhythmia, uncontrolled congestive heart failure or acute myocardial infarction within the previous six months; history of uncontrolled diabetes mellitus (stable insulin dose and/or stable oral hypoglycemic agent permitted); or have planned chemotherapy or radiation during the 7 days following study initiation.
- In addition, women of childbearing potential must consent to use adequate contraception throughout protocol therapy; females of childbearing potential must have a negative urine pregnancy test ≤7 days prior to registration.

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians

should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness that would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial.

Patient Registration/Randomization

Patient registration can occur after pre-treatment evaluation is complete, eligibility criteria have been met, and the patient must has signed the informed consent.

Contact the Study Chair or Registration Specialist who will have the patient registered into the study and have the patient randomized. After the treatment assignment has been ascertained, the patient's study medication code number will be used to confirm the registration.

To ensure both the patient and the medical professionals who care for the patient are blinded to the identity of the treatment assignment, the Registration Specialist will follow a double-blinding procedure. The pharmacist or designated contact person at the treating site will maintain records that indicate the identity of the patient and their corresponding study medication code number.

Study Calendar

	Prior to Registration	Days 1-7	Day 8
Tests & Observations			
History and physical, weight, ECOG PS,	X		
and complete demographics (Appendix I)	X		
Nurse phone call (record per Appendix IV)		X[3]	X[3]
Baseline and Daily Questionnaire and Vomiting Assessment (Appendix II)	X[1]	X[2]	X[2]
FACT-G (Quality of Life) (Appendix III)	X		X
Well Being Assessment (Patient and Investigator)(Appendix II)	X		X
Serum or Urine HCG	X[4]		
Creatinine, SGOT,SGPT, ANC	X[5]		

1 To be completed by patient after registration and prior to treatment.
2 Patient to complete daily on days 1-8.
3 Nurse/Research Coordinator will contact each patient each day (days 2-8) to remind the patient to complete forms, answer questions, and to query adverse events. Please try to call the patient around the same time of day as the study drug was given on day 1 (+/- 1 hour).
4 For women of childbearing potential, must be done ≤7 days prior to registration.
5 To be completed ≤120 days prior to registration.

Data Collection and Submission

The data collection will be via forms completed by the patient, the investigator, and the research nurse on days 1 to 8 during the study. The forms will be submitted via fax or e-mail to the Study Chair.

Treatment Plan/Intervention

Protocol treatment is to begin ≤14 days of registration. Protocol therapy will be instituted daily for seven days. Patients will be permitted to take rescue therapy (treating investigator's choice) anytime during the seven day treatment period based on the evaluation of the treating investigator for nausea and/or emesis/retching, based on clinical circumstances.

Definitions of Deviations in Protocol Performance

Major Deviations

A "major deviation" is a situation in which patient safety or outcome is compromised.

Minor Deviations

A "minor deviation" is a discrepancy from the protocol that is not of sufficient magnitude to prevent adequate evaluation of the patient and does not cause the patient to be excluded from the statistical evaluation.

Data Collection and Forms

The patient will complete the Baseline and Daily Questionnaire and Vomiting Assessment on day one prior to the start of treatment and on days 2-8 at the same time of day as the protocol therapy.

Dose and Treatment Modifications, Unblinding

Ancillary therapy, concomitant medications, and supportive care

Patients should receive full supportive care while on this study, as determined to be appropriate by their attending clinicians.

Dose Modifications

If the patient experiences a significant adverse event (per patient and physician discretion) felt to potentially be related to the study product (olanzapine/placebo), then the study product should be stopped and this should be recorded.

Unblinding Procedures

Protocol-specified Unblinding:

Trial participants may be unblinded upon completion of protocol therapy and submission of all of their questionnaire results. Any potential toxicity of the study agent (olanzapine/placebo) needs to be determined and recorded prior to unblinding of the investigator and/or patient. Contact the Study Chair during regular business hours.

Emergency Unblinding Procedures:

A trial participant's treatment assignment can be unblinded in emergent situations with the approval of the Study Chair (or designee) only if unblinding would influence management of the situation, e.g., if a child has swallowed a vial of pills.

Adverse Events

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

Solicited adverse events: None, other than those collected by the daily patient completed questionnaire, which will include drowsiness.

Expedited adverse event reporting

Investigators are required by Federal Regulations to report serious adverse events as defined below. Investigators are required to notify the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the CTEP Adverse Event Reporting System (CTEP-AERS). The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for reporting. The CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All treatment areas should have access to a copy of the CTCAE version 4.0. A copy can be downloaded from the CTEP website http://ctep.cancer.gov.

Be sure to read this entire protocol section, as requirements are described in both the table and bullet points following the table. In the case of a conflict, the additional instructions or exclusions supersede the table.

Informed Consent

All patients must give written informed consent, and the study must be approved by the institutional review committees of each participating site (Appendix V).

Study Design and Treatment Regimen.

All patients eligible for the study will be randomized to receive olanzapine (5.0 mg/day, orally, days 1 to 7) or a placebo (orally, days 1 to 7). Randomization will be stratified by gender.

The protocol dose of olanzapine was determined from the various studies in the literature (13, 21-28, 30-34). Although 10 mg/day for four days has been the commonly used olanzapine dose, in combination with other antiemetics, in studies for the prevention of chemotherapy-induced nausea and vomiting (30-34), a 5 mg/day dose was chosen for this pilot trial as this lower dose has been used in case reports for the treatment of chronic nausea in the literature (21-28) and by Alliance Symptom Intervention committee members in clinical practice, with perceived efficacy and with little to no toxicity.

The study treatment will be 7 days and study duration will be 8 days. Patients will be permitted to stop the assigned antiemetic treatment at any time during the 7 days and change to an alternative antiemetic treatment (any rescue therapy as determined by the patient's physician) if the patient has persistent nausea and/or emesis/retching that has not responded to the assigned antiemetic treatment. Patients may request rescue or a patient's physician may determine rescue is necessary at any time during the 7 day period. Patients will not necessarily be taken off study after rescue therapy is initiated.

When the patient has completed their study period (i.e., 8 days), including all required questionnaires, they can be unblinded. **If they were on the placebo, we will give them a supply of olanzapine to try (assuming that they want to try this).**

If a patient has continued substantial nausea and/or vomiting after being on the study for 2 days, they can choose to stop the study. They can be unblinded after they and the nurse have completed all the study questionnaires (so that more accurate attribution can be made prior to unblinding).

Study Visits and Assessment Procedures

In the pre-study period, all pertinent demographics (e.g. age, gender, height, weight) and appropriate medical data (e.g. site and stage of disease, ECOG PS, laboratory values, medications and present therapies including present oncologic therapy) will be recorded. The investigator will be asked to record their best estimate of the primary clinical etiology (medications (opioids), delayed gastric emptying, partial bowel obstruction, vestibular dysfunction, metabolic issues, anxiety, and depression) of the chronic nausea prior to study entry.

Patient-reported outcomes (PROs) will be the primary means for measuring the study endpoints. The major end points of the study will be nausea (0-10, visual analogue scale) and /or episodes of vomiting, day 1 pre-treatment and days 2-8 post treatment initiation.

Extensive reviews of the assessment of chronic nausea and emesis in patients with advanced cancer have suggested the use of a visual analogue and a categorical scale to assess key symptoms (appetite, nausea, fatigue, pain), vomiting, and quality of life (11, 13, 29-34, 38). After patients give informed consent and after demographic information is obtained (Appendix I), patients will have a baseline assessment which will include assessment of symptom intensity (appetite, nausea, fatigue, sedation, pain) and vomiting in the previous 24 hours (Appendix II), and assessment of quality of life (QOL) (Appendix III). The five symptoms will be measured on a visual analogue scale (0-10) (0 = symptom absent, 10 = worst possible symptom). The number of vomiting episodes in the preceding 24 hours will be recorded. Well-being will be estimated on a 0-10 numerical scale (0 = best possible, 10 worst possible) (Appendix II). QOL will be measured by the Functional Assessment of Cancer Therapy-General (FACT-G) instrument (Appendix III), a well-established QOL instrument consisting of 27 questions grouped into four domains (39).

The study duration for the primary endpoint will be 8 days. Each day, the patients will estimate the intensity of their appetite, nausea, fatigue, sedation, and pain using the numerical visual analogue scale, and record the number of vomiting episodes in the previous 24 hours. The patient will also record the use of the daily dose of the study drug in a medication log as well as the use of any rescue medications.

On day 8, the patient will complete the last daily dairy (to capture day 7 data) and will estimate the quality of life with the FACT-G instrument, and both the patient and the investigator will assess the patients' well-being, using the 0-10 numerical scale.

The patient will be asked to complete the forms at approximately the same time each day. To facilitate patient-completion of these PRO tools, a Nurse/Research Coordinator will contact each

patient each day (days 2-8) to remind the patient to complete forms, answer questions, and to query toxicities.

V. Statistical Considerations

This is a randomized, placebo-controlled, pilot study to determine the effect of olanzapine on chronic nausea and/or vomiting in cancer patients. Patients will be randomly assigned to receive either olanzapine or placebo at a 1:1 ratio and stratified based on gender. The primary endpoint is the change in nausea scores from baseline to 24 hours of treatment using the Visual Analogue Scale. Secondary endpoints include daily nausea and vomiting scores, daily episodes of vomiting/retching (number and time), the utilization of rescue therapy, and toxicities of olanzapine as measured by PRO questionnaires and CTCAE v4.0.

The primary objective of this pilot trial is to estimate the effect of olanzapine on chronic nausea and vomiting to inform future design of a randomized phase III clinical trial. Descriptive statistics and statistical plots will form the foundation of statistical analysis for this trial. We will summarize the study endpoints by mean (SD), median (inter-quartile range), and frequency (percentage). Nausea change scores will be compared between arms using a two-sample t-test or a Wilcoxon rank sum test as appropriate. If the two-sided p value is less than 0.05, then we will consider this to be supportive of a statistically significant advantage for olanzapine in this situation. If the p value is 0.2 or better, in the correct direction, then this would support further study in a larger phase III trial. The difference in nausea change scores from baseline to 24-hours post treatment between the two arms will be estimated along with a 95% confidence interval. We will plot the repeated measurements of nausea and vomiting longitudinally to explore the pattern over time and difference between treatment arms. Because of exploratory nature of this pilot study, we will not adjust for multiple comparisons. Due to the logistical and financial constraints, the total sample size will be fixed at 30 patients, 15 patients per arm. Assuming a 10% drop-out due to ineligible patients, cancellations, and major violations, we expect to have 13 patients per arm evaluable for the primary endpoint. As this is a pilot trial with a limited sample size with the primary goal of exploring the effect of olanzapine on nausea, no formal power analysis was conducted. Assuming an accrual rate of 3 patients per month, the patient accrual will be completed in 10 months, and analysis will be performed approximately 3 months following accrual completion.

VI. Investigator Roles

Rudy Navari will act as the senior investigator and will mentor Eric Roeland, a promising younger investigator.

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VIII. Appendices

Patient study number and initials:_____

Appendix I: Demographics:

Date: _____/_____/_____

Age: _____**years**

Gender: ___**Male** ___**Female**

Site/Stage of Disease: _____

ECOG PS: _____**I** ____**II**____**III**____**IV**

LAB:

Serum Creatinine:	_____	≤2.0 mg/dL
SGOT or SGPT:	_____	≤3 x upper limit of normal (ULN)
Absolute neutrophil count:	_____	≥1500/mm^3

Suspected etiologies of Chronic Nausea/Vomiting (check all that apply):

___**medications;**

___**delayed gastric emptying;**

___**partial bowel obstruction;**

___**vestibular dysfunction;**

___**metabolic issues;**

___**anxiety;**

___**depression;**

___**tumor burden;**

___other (please specify):

_____

_____

Patient study number and initials:_____

Appendix II

BASELINE AND DAILY QUESTIONNAIRE

Date: ____/____/_____

A. Linear Analogue Scale

For the following questions, please circle the one number (0-10) that best describes the way you felt over the past 24 hours.

1. Please rate your nausea over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No nausea at all										Nausea as bad as it can be

2. Please rate your appetite over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No appetite at all										Appetite as good as it can be

3. Please rate your fatigue over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No Fatigue at all										Fatigue as bad as it can be

4. Please rate your sedation over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No sedation at all										Sedation as bad as it can be

5. Please rate your pain over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10
No pain at all										Pain as bad as it can be

6. Please rate your well-being over the past 24 hours

0	1	2	3	4	5	6	7	8	9	10

Well-being as worse as possible

Well-being as good as possible

B. Vomiting Assessment

For the past 24 hours, please check one option in each box:

	*Vomiting (check one)	Number of extra nausea/vomiting pills (aside from the study pill) taken because you developed nausea/vomiting
Last 24 hours	__None __Once Time: _____ __More than once Times: _____ _____ _____ _____ _____ _____ _____ _____ _____	__None __One __Two __More than two

*A single vomiting episode is defined as:

- a single vomit of solid or liquid stomach contents
- a single retch, or 'dry heave', that did not produce solid or liquid stomach contents
- any episode of continuous vomiting or retching

Note: Episodes separated from each other by the absence of retching or vomiting for at least 1 minute should be considered separate emetic episodes.

Patient study number and initials:_____

Appendix III FACT G

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

PHYSICAL WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Patient study number and initials:_____

Appendix IV Nurse Daily Contact Form

Study day of call (circle one) : 1 2 3 4 5 6 7 8

Date of call: _____

Did the patient take the study medication (olanzapine or placebo) today : Yes No

Did the patient ascribe any toxicities to the study drug: No__ Yes__; if yes, please describe:

Did the patient take any additional medication to try to control nausea or vomiting: Yes No
If yes, please complete the table below:

Agent	Dose	Route

APPENDIX V CONSENT FORM

NCI Consent Form Template Version Date: May 12, 2013

NOTES FOR LOCAL INVESTIGATORS*:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, of the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/

- A blank line, "_____", indicates that the local investigator should provide the appropriate information before submitting to the Institutional Review Board.

*These notes for investigators are instructional and should not be included in the consent form sent to Institutional Review Boards.

Study Title for Study Participants: OLANZAPINE FOR THE TREATMENT OF CHRONIC NAUSEA AND/OR VOMITING, UNRELATED TO CHEMOTHERAPY OR RADIATION, IN ADVANCED CANCER PATIENTS – A PILOT, DOSE-FINDING TRIAL.

You are being asked to participate in this study because cancer and its related side effects can cause the side effect of nausea and vomiting. People who do not take part in this study will receive standard medications that have been approved by the Food and Drug Administration for nausea and vomiting.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available

Why is this study being done?

You have cancer that may cause nausea and vomiting. The purpose of this study is to test whether olanzapine can reduce nausea and vomiting. Olanzapine is a medication which has been approved by the Federal Drug Administration (FDA) for the treatment of specific mental illnesses and has been used in many patients over the past 15 years, but it is not FDA approved to treat nausea and vomiting. Over the past five years, it has been demonstrated in multiple scientific studies involving small numbers of patients to have anti-nausea and anti-vomiting effects in patients receiving chemotherapy. The purpose of this study is to determine if the use of this medication can significantly reduce nausea and vomiting in a large number of patients with cancer who have

nausea/vomiting troubles, not related to chemotherapy. The effects of olanzapine will be compared to a placebo. A placebo is a pill that looks like the study drug but contains no medication. There will be about 30 people taking part in this study.

What are the study groups?

This study has two study groups. Group 1 will receive the study drug olanzapine and Group 2 will receive a placebo, a pill that looks like the study drug but contains no medication.

A computer will, by chance, assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other.

This study has two study groups.

- Group 1 will get a study drug called olanzapine (10 mg orally on days 1 to 7).
- Group 2 will get a placebo orally on days 1 to 7.

How long will I be in this study?

You will receive the olanzapine or placebo for 7 days. After you finish the daily oral olanzapine or placebo for seven days, your doctor will continue to watch you for side effects for an additional day.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests that you will need to have if you take part in this study.

Before you begin the study:
You will need to have the following tests to find out if you can be in the study:

- Review of your medical history
- Physical examination including height, weight, performance status evaluation (ability to perform daily functions)
- Review of your current and past medications
- Standard blood tests (approximately 3 tablespoons of blood will be drawn). These will not have to be repeated if they have been done within the last 3 months, which is likely in most patients
- Pregnancy test if you are a woman of childbearing potential

During the study:

- You will be completing patient questionnaires on day 1 prior to treatment and at approximately the same time as your treatment was given each day for the next seven days. You will be asked to complete a one page short questionnaire on the amount of nausea, vomiting, and/or sedation you have experienced in the previous 24 hour period. The questionnaire should take less than 5 minutes to complete each day.

What possible risks can I expect from taking part in this study?

Likely Side Effects of Olanzapine (when taken for 7 days):

Most of the studies that have been done with 7 days of olanzapine have reported that the only evident side effect has been sedation (sleepiness). Below are listed side effects associated with this medication when it is taken for several weeks to months.

Possible Side Effects of Olanzapine (when taken for weeks to months)

COMMON, SOME MAY BE SERIOUS In 100 people receiving olanzapine, more than 20 and up to 100 may have:
• Blurred vision, arm and leg swelling, restlessness, tingling of the hands and feet

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving olanzapine, from 4 to 20 may have:
• Sedation (sleepiness, muscle stiffness, mask-like face, impaired vision, and difficulty swallowing)

RARE, AND SERIOUS In 100 people receiving olanzapine, 3 or fewer may have:
• Bladder pain, bruising, headache, lower back pain, muscle tension

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study drug(s)/ approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, Institutional Review Board or the Food and Drug Administration.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the Institutional Review Board or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The olanzapine/placebo will be supplied at no charge while you take part in this study. It is possible that the olanzapine/placebo may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study.

Participant's signature_____

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____