TREATMENT OF REFRACTORY NAUSEA
URCC16070
NCT03367572

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Participating Institutions:

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IND: NA

Agent(s)/Supplier: Prochlorperazine (Compazine®), olanzapine (Zyprexa®), and dexamethasone will be supplied by the University of Rochester Investigational Drug Service (IDS). Netupitant/palonosetron (Akynzeo®) will be supplied by Helsinn Therapeutics (U.S.) Inc., of Iselin, New Jersey

Packaged and distributed by: University of Rochester Investigational Drug Service

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Protocol Contact Information

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For regulatory requirements:	For patient enrollments:	For data submission:
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-CTSU (2878) to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for detailed instructions.	Data collection for this study will be done through REDCap. All data and REDCap questions should be directed to: **URCC NCORP Research Base** Protocol Coordinator: URCC_16070@urmc.rochester.edu URCC NCORP Research Base Saunders Research Building 265 Crittenden Blvd Box 658 Rochester, NY 14642 Do **not** submit study data or forms to the CTSU. Do **not** copy the CTSU on data submissions. Refer to the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program – Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

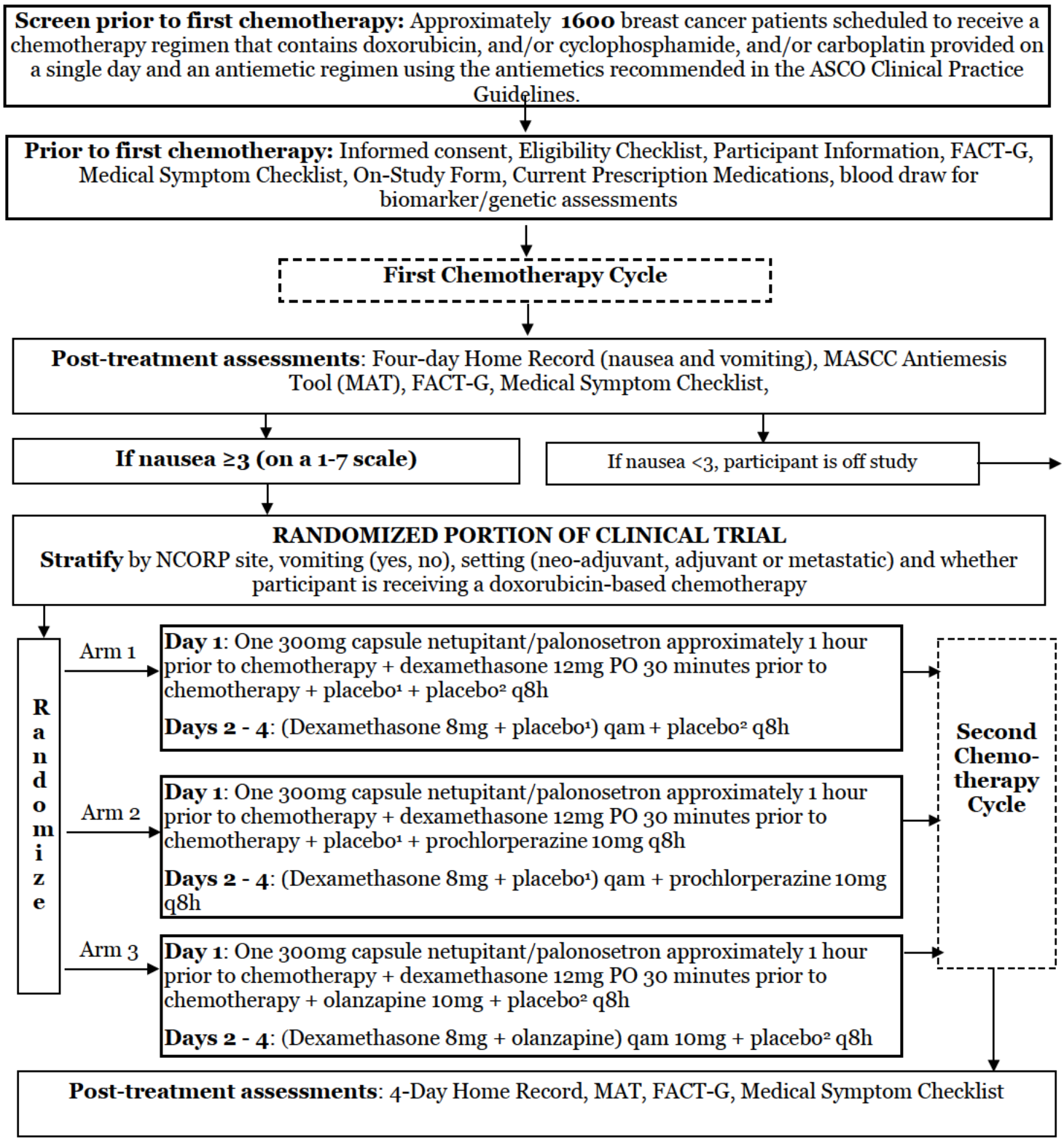
For **URCC Research Base regulatory questions**, contact URCC_Regulatory@urmc.rochester.edu.
For **adverse event reporting** contact URCC_16070@urmc.rochester.edu.

All study supplies will be distributed from URCC. Supplies can be ordered by contacting the Protocol Coordinator at URCC_16070@urmc.rochester.edu.

For questions regarding the URCC NCORP website, contact URCC_Techsupport@urmc.rochester.edu.

For clinical questions (i.e. patient eligibility or treatment-related):
URCC_16070@urmc.rochester.edu
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)
Contact the CTSU Help Desk by phone or email:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

SCHEMA



Note: Placebo¹ matches olanzapine and placebo² matches prochlorperazine.

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1. INTRODUCTION AND BACKGROUND

1.1 Rationale

Chemotherapy-Induced Nausea Remains a Significant Problem: Despite the provision of antiemetic regimens in accordance with the American Society of Clinical Oncology (ASCO) guidelines,(1) chemotherapy-related nausea remains a significant issue and is rated by patients as a greater problem than vomiting.(2-8) Nausea following chemotherapy is also three times more likely to occur than vomiting.(9) The three major antiemetic guidelines focus almost exclusively on vomiting or on nausea and vomiting combined.(1,10,11) There is little information provided specifically for nausea control and an absence of clear guidelines on which antiemetic regimen to give patients who have already experienced nausea at a prior chemotherapy cycle.

Nausea remains one of the most troublesome and frequent side effects associated with cancer treatment.(2-5,12-17) It is a widespread problem that causes extreme discomfort and seriously impairs QOL,(18,19) and it negatively affects patients' nutritional habits, ability to work, and motivation to follow recommended treatment regimens.(18-21) The introduction of the 5-HT_3 RA class of antiemetics (e.g., granisetron) more than 15 years ago reduced treatment-related vomiting, but not treatment-related nausea.(2,3,13-15) More recently, the use of palonosetron (Aloxi), a second-generation 5-HT_3 RA, and aprepitant (Emend®), a neurokinin-1 receptor antagonist), have further increased control of emesis; treatment-related nausea, however, remains a significant problem.(4,6,7,17,22,23) Our recently completed multi-center antiemetic study on optimal treatment for nausea conducted by the URCC CCOP (now NCORP) Research Base showed that nausea remains a significant problem and that more effective regimens for controlling nausea are needed.(9) Over half the patients studied experienced nausea, and control afforded by all of the antiemetic regimens examined was inadequate.

Current ASCO guidelines for refractory chemotherapy-induced nausea and vomiting (CINV) suggest that oncologists consider adding olanzapine (Zyprexa®) or a dopamine antagonist such as prochlorperazine (Compazine®) to the antiemetic regimen, but these are only two of many possible strategies for control of refractory CINV**.**(1) We chose to examine the efficacy of prochlorperazine in the present proposal because it is suggested for control of refractory CINV in both the ASCO(1) and National Comprehensive Cancer Network (NCCN)(11) antiemetic guidelines and because of our very positive experience with it in Preliminary Studies 1 and 2, described later. We chose to study olanzapine because it too is suggested for control of refractory CINV in both the ASCO and NCCN antiemetic guidelines and also because of the positive findings from the recently closed Alliance Group study of olanzapine for the prevention of CINV(24) and also the very positive systematic review of six randomized clinical trials evaluating olanzapine for CINV.(25)

Current Multinational Association for Supportive Care in Cancer (MASCC) guidelines do not discuss optimal treatments for nausea in patients with nausea following a previous cycle and do not recommend any specific treatment for recurrent emesis, although they do say that "rotation of antiemetics within a given family of antiemetic agents would be unlikely to lead to additional benefit."(10) ASCO guidelines for refractory vomiting suggest that clinicians should consider adding lorazepam, alprazolam, a dopamine antagonist or olanzapine to the regimen or substituting high-dose intravenous metoclopramide for the 5-HT_3 antagonist.(1) The current protocol represents a rigorous examination of the benefits of incorporating either olanzapine or a dopamine antagonist (i.e., prochlorperazine) to the Cycle 2 antiemetic regimen of patients who experienced emesis or nausea despite optimal prophylaxis at Cycle 1.

In addition, this study will provide important data on factors related to the occurrence of nausea and on optimal control of nausea in breast cancer patients receiving moderately or highly emetogenic chemotherapy. As we move to an age of more patient-centered medicine, it is easy

to see how individualized treatment regimens based on patient characteristics will enable oncologists to pick the appropriate antiemetic regimen for their individual patients, and the nausea algorithm we seek to develop could lead to a more personalized medicine by providing the information necessary for modifying antiemetic regimens based upon individual risk factors. This algorithm could lead to an empirically based personalized medical approach for control of chemotherapy-induced nausea.

Approach: The study consists of two parts with screening and some assessments occurring at baseline and chemotherapy Cycle 1 and the randomized portion of the study (N = 333) occurring at Cycle 2. During Cycle 1, we will screen and consent chemotherapy naïve breast cancer patients about to begin a chemotherapy regimen that contains doxorubicin, and/or cyclophosphamide, and/or carboplatin. All three of the drugs are commonly given and all have at least moderate emetogenic potential. A key inclusion criterion will be that all patients must be scheduled to receive antiemetic drugs recommended in the ASCO guidelines.(1) We anticipate needing to screen approximately 1600 patients, or more if necessary, to meet our Cycle 2 target number. The Cycle 2 portion will be conducted in those participants who experience moderate or greater nausea at Cycle 1 despite the recommended antiemics prescribed at Cycle 1. It will be a Phase III randomized, double-blinded, placebo-controlled, 3-arm study (N = 333) that builds upon our prior CINV studies and investigates optimal control of CINV in patients who experienced CINV following initial chemotherapy. At Cycle 1, all rescue medications will be allowed for uncontrolled chemotherapy-induced nausea and vomiting (CINV). At Cycle 2, only the study agents can be taken for CINV. For breakthrough nausea and vomiting at Cycle 2 all rescue medications with the exception of metoclopramide and lorazepam will be allowed. We note that these two antiemetics are not allowed because benzodiazepines and anticholinergics are excluded from the protocol. We will document the type and days when prescribed rescue medications were taken.

Design Considerations

- We include a CINV assessment, but no intervention at Cycle 1, to provide baseline information on CINV for patients who are randomized at Cycle 2. It will also allow us to assess the actual levels of CINV in breast cancer patients from moderately and highly emetogenic chemotherapy when ASCO guideline antiemetics are provided.(1)

- Arm 1 will be the control condition. In this study arm, participants will receive Akynzeo® with dexamethasone along with appropriate placebos. We note that Akynzeo® is an oral, fixed combination of an NK1 receptor antagonist (netupitant) and a 5-HT_3 receptor antagonist (palonosetron) in a single capsule. It was approved by the U.S. Food and Drug Administration to treat nausea and vomiting in patients undergoing cancer chemotherapy in October 2014 and added to the ASCO antiemetic treatment guidelines in January 2015.

- An important consideration in choosing Akynzeo® for the control condition rather than continuing with the combination of aprepitant and palonosetron that most participants would have received at Cycle 1 was to ensure that no patient would be randomized to the same medication at Cycle 2 that failed to control their CINV at Cycle 1. To ensure this, we have excluded patients receiving Akynzeo® at Cycle 1 from participating in the study. We note that while aprepitant and netupitant are both NK1 receptor antagonists, they differ significantly in that netupitant has a substantially longer half-life at approximately 80 hours than aprepitant at 9-13 hours.

- We chose to study olanzapine because it is suggested for control of refractory CINV in both the ASCO and NCCN antiemetic guidelines and also because of a recent very positive systematic review of six randomized clinical trials evaluating olanzapine for CINV(25) as well as the positive findings from the recently closed Alliance Group study of olanzapine for the prevention of

CINV.(24) We note that the latter study examined prevention of CINV at Cycle 1 of chemotherapy and not treatment of refractory CINV as we propose.

- We chose to examine the efficacy of prochlorperazine in the present proposal for four reasons: 1) because of our very positive experience with it in Preliminary Studies 1 and 2, described in Section 1.2, 2) the fact that as a dopamine antagonist, prochlorperazine employs a method of action for control of nausea that is different from those of the netupitant, palonosetron and dexamethasone, and that may be additive to those agents, 3) its more than five-decade history as a widely used and very effective antiemetic in the cancer environment, and 4) its inclusion in the current ASCO guidelines as a suggestion for treating refractory vomiting(1).

- We chose to prescribe prochlorperazine q8h rather than prn because the q8h dosing was more effective than prn dosing in preliminary study 1, and also because the NCCN antiemetic Guidelines recommend routine around-the-clock administration of antiemetics rather than PRN for refractory nausea.(11)

- We chose to extend the study medication (i.e., olanzapine/prochlorperazine), as well as dexamethasone, to include Day 4 at Cycle 2 because our data in Preliminary study 2 showed that 38.3% of breast cancer patients who experienced peak nausea of $\geq$ 3 (scale = 1-7) during any of days 1-3 of chemotherapy also experienced nausea at a level $\geq$ 3 on Day 4. We note that having a peak nausea level $\geq$ 3 at Cycle 1 is a key eligibility criterion for the randomized portion of the current study.

- We chose to limit eligibility to breast cancer patients to make the sample as homogeneous as possible while still keeping the study clinically meaningful. This patient group has greater nausea than most if not all other large patient groups.(26)

- We chose to collect blood at baseline on participants for exploratory analyses to further elucidate the possible relationship between glutathione metabolism and CINV(27) as well as to bank blood for exploratory analyses examining germline genetic markers that might help identify subgroups of patients at high risk for development of cancer-related or treatment-related side effects as well as subgroups most likely (or least likely) to respond to a particular antiemetic regimen.(28) We note that we are not specifying any specific genetic markers at this time, but will monitor the field closely over the next several years as we collect the samples in order to target the most relevant genetic markers when we do the analyses several years from now.

- We originally predicted 1) that approximately 40% of subjects from Cycle 1 would meet all the eligibility criteria for Cycle 2 and 2) that 90% of eligible subjects would participate in Cycle 2. While our first prediction was accurate, our second prediction was not. Our assumption was that 100% of subjects eligible for Cycle 2 would participate, but the participation rate was only approximately 63% among the first 500 subjects enrolled to Cycle 1 and meeting the Cycle 2 eligibility. Therefore, it is necessary to increase our originally planned accrual for Cycle 1 from 800 subjects to 1,200 subjects. This is necessary to meet our accrual goal of 333 subjects completing Cycle 2.

1.2 Literature Review and Preliminary Studies

Preliminary Study 1 was conducted between 2001 and 2004 in 671 chemotherapy-naïve patients receiving chemotherapy containing doxorubicin.(29) All patients were given a first generation 5-HT_3 RA antiemetic plus dexamethasone on the day of treatment (Day 1) and randomized to one of three regimens for Days 2 and 3: Group 1 – prochlorperazine 10 mg p.o. every 8 hours; Group 2 – any first generation 5-HT_3 RA using standard dosage; or Group 3 – prochlorperazine 10 mg p.o. as needed. No corticosteroids were given on Days 2 and 3 of treatment. The study was

designed to determine if a 5-HT_3 RA antiemetic was more effective than prochlorperazine in controlling DN. There was no difference between the groups in mean or maximum delayed nausea (DN) severity. Patients taking prochlorperazine regularly were least likely to report DN (71% vs. 79% [Group 2] and 82% [Group 3], $p<0.05$).

Preliminary Study 2 tested four antiemetic regimens for control of DN following chemotherapy containing a platinum-based drug or an anthracycline in 1021 chemotherapy-naïve patients and was conducted from 2007 to 2010.(9) Group 1 of the prior study was included as a comparator group, and new groups to examine regimens containing palonosetron, aprepitant, and/or dexamethasone were added. We found that the addition of dexamethasone on Days 2 and 3 reduced DN and the beneficial effect of adding aprepitant for control of DN was the same as adding prochlorperazine.

1.3 Study Medications

The following two antiemetic medications are provided to some randomized participants during Cycle 2: Prochlorperazine (Compazine®), Olanzapine (Zyprexa®). Details on the medications are provided in Sections 5.4 and 8.

1.4 Feasibility

A key advantage to conducting this study within the NCORP network is the demonstrated track record of this group in recruiting patients prior to initial chemotherapy as evidenced by both Preliminary Studies 1 and 2 meeting their accrual goals. Other relevant factors related to NCORP are: 1) NCORP Community Sites and Minority/Underserved Community Sites have been involved in developing this protocol, 2) Interest was high with our NCORP affiliates as determined by discussion at our annual NCORP Research Base meeting in September 2015, 3) all accrual will take place at NCORP sites, and 4) the University of Rochester NCORP (previously URCC CCOP) Research Base has conducted five previous chemotherapy-induced nausea and vomiting (CINV) studies (total N = 3,365), all of which met their accrual targets.

2. AIMS/OBJECTIVES

2.1 Primary Aim is to determine if control of nausea at Cycle 2 in participants who experienced CINV at Cycle 1 is improved by the addition of either prochlorperazine or olanzapine to the control arm of netupitant, palonosetron and dexamethasone.

2.1.1 Hypothesis 1: Control of **nausea** at Cycle 2 in participants who experienced CINV at Cycle 1 despite receiving an ASCO-recommended antiemetics(1) can be improved by the addition of either prochlorperazine or olanzapine to the standard antiemetic combination of netupitant, palonosetron and dexamethasone.

2.2 Secondary Aim 1 is to determine if olanzapine is more effective than prochlorperazine in controlling nausea at Cycle 2 in participants who experienced CINV at Cycle 1 when used in combination with netupitant, palonosetron and dexamethasone.

2.2.1 Hypothesis 2: Olanzapine, which is a newer antiemetic drug with a more problematic side-effect profile than prochlorperazine, is more effective than prochlorperazine in controlling **nausea** when used in combination with netupitant, palonosetron and dexamethasone.

2.3 Secondary Aim 2 is to determine if control of vomiting at Cycle 2 in participants who experienced CINV at Cycle 1 is improved by the addition of either prochlorperazine or olanzapine to the control arm of netupitant, palonosetron and dexamethasone.

2.3.1 Hypothesis 3: Control of **vomiting** at Cycle 2 in participants who experienced CINV at Cycle 1 despite receiving an ASCO-recommended antiemetic regimen(1) can be improved by the addition of either prochlorperazine or olanzapine to the standard antiemetic combination of netupitant, palonosetron and dexamethasone.

2.4 Secondary Aim 3 is to determine if olanzapine is more effective than prochlorperazine in controlling vomiting at Cycle 2 in participants who experienced CINV at Cycle 1 when used in combination with netupitant, palonosetron and dexamethasone.

2.4.1 Hypothesis 4: Olanzapine, which is a newer antiemetic drug with a more problematic side-effect profile than prochlorperazine, is more effective than prochlorperazine in controlling **vomiting** when used in combination with netupitant, palonosetron and dexamethasone.

2.5 Exploratory Aim 1 is to create an empirically-based algorithm predicting nausea from breast cancer chemotherapy regimens that takes into account not only state-of-the-art antiemetic regimens but also participant factors such as age, race, education, ethnicity, QOL, alcohol consumption, susceptibility to nausea, expectancy, anxiety, level of nausea on the day prior to treatment, and prior history of nausea.

2.6 Exploratory Aim 2 is to compare the effects of the interventions on QOL, as assessed by the FACT-G, by following the same procedures described under the Primary Aim and the first Secondary Aim, using change in the FACT-G scores as the response.

2.7 Exploratory Aim 3 is to provide preliminary data on the frequency and severity of sleep disturbance, fatigue, anxiety, and dizziness, across treatment conditions.

2.8 Exploratory Aim 4 is to provide preliminary data on biological factors (e.g. GSH recycling, genetic markers) that may help identify a subgroup of participants at high risk for development of cancer-related or treatment-related side effects, or response to treatment.

3. CHARACTERISTICS OF STUDY POPULATION

3.1 Inclusion Criteria for Participation in the Cycle 1 Portion of the Study

Participants must:

3.1.1 Have a diagnosis of breast cancer and be chemotherapy naïve. Note: Prior methotrexate for non-cancerous conditions is allowed.

3.1.2 Be scheduled to receive a **single-day** chemotherapy regimen that contains doxorubicin, and/or cyclophosphamide, and/or carboplatin. Single-day chemotherapy is defined as **only one infusion or injection per cycle.** Herceptin® (trastuzumab) and other chemotherapy agents will be allowed with any of these regimens.

3.1.3 Be scheduled to receive an antiemetic regimen that does not contain Akynzeo®.

- For chemotherapy regimens with a high emetic risk, the antiemetic regimen must include an NK-1 antagonist receptor, a 5HT3 receptor antagonist and dexamethasone. Other antiemetics, including additional dexamethasone and olanzapine, may also be included at cycle one.
- For chemotherapy regimens with a moderate emetic risk, the antiemetic regimen must include a 5HT3 receptor antagonist and dexamethasone. Other antiemetics, including additional dexamethasone and olanzapine, may also be included at cycle one.

3.1.4 Be able to read English. Materials will not be provided in Spanish because validated translations of most of the study measures are not available in Spanish, and Spanish translating capacity is not available at all affiliate sites.

3.1.5 Be at least 18 years of age.

3.1.6 Be female.

3.1.7 Have the ability to give written informed consent.

3.1.8 Have ECOG performance status of 0, 1, or 2

3.1.9 Note: Because the NCCN antiemetic guidelines (11) state that olanzapine should be used with caution in elderly patients, patients 80 years of age or older must have approval from an oncologist or their designee to participate in this study.

3.1.10 Note: Because aprepitant can lower International Normalized Ratio (INR) levels if taken concurrently with warfarin, patients currently receiving warfarin must have approval from an oncologist or their designee to participate in this study.

3.1.11 Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control, or abstinence) for the duration of the study and have a negative pregnancy test within 10 days prior to the initiation of chemotherapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

3.2 Additional Inclusion Criteria only for the Participants Advancing to the Cycle 2 Portion of the Study

Participants must:

3.2.1 Only participants with a nausea score $\geq$ 3 at least once on the 4-day home record from Cycle 1 can be randomized for Cycle 2.

3.2.2 Participants must be scheduled to receive the same chemotherapy regimen as received at Cycle 1.

3.2.3 Because quinolone antibiotic therapy can increase the level or effect of olanzapine by altering drug metabolism and thereby potentially increase risk of side effects, patients currently receiving quinolone antibiotic therapy must have approval from an oncologist or their designee to participate in the Cycle 2 portion of the study. (A partial list of quinolone antibiotics is included in the supporting documents section of the protocol webpage.)

3.3 Exclusion Criteria for Participation in the Cycle 1 Portion of the Study

Participants must not:

3.3.1 Have clinical evidence of current or impending bowel obstruction.

3.3.2 Have a known history of central nervous system disease (e.g., brain metastases or a seizure disorder.)

3.3.3 Have dementia.

3.3.4 Have uncontrolled diabetes mellitus or uncontrolled hyperglycemia.

3.3.5 Have severe hepatic impairment, severe renal impairment, or end-stage renal disease as determined by the treating physician.

3.3.6 Have had long-term treatment (> 5 days within the past 30 days) with an antipsychotic agent such as risperidone, quetiapine, clozapine, a phenothiazine, or a butyrophenone within 30 days before enrollment or plans for such treatment during the study period. Note: Participants could have received prochlorperazine and other phenothiazines as antiemetic therapy on a short term basis (i.e., ≤ 5 days). (A partial list of antipsychotic agents is included in the supporting documents section of the protocol webpage.)

3.3.7 Have a known cardiac arrhythmia, uncontrolled congestive heart failure, or acute myocardial infarction within the previous 6 months.

3.3.8 Be taking benzodiazepines regularly (> 5 days within the past 30 days). PRN use (≤ 5 days) for the short-term relief of the symptoms of anxiety, anxiety associated with depressive symptoms, or as a rescue medication for breakthrough CINV is allowed. (A partial list of benzodiazepines is included in the supporting documents section of the protocol webpage.)

3.3.9 Be taking anticholinergic medications. (A partial list of anticholinergic medications is included in the supporting documents section of the protocol webpage.)

3.3.10 Be taking amifostine (Ethiofos).

3.3.11 Have a known hypersensitivity to olanzapine or to phenothiazines.

3.4 Additional Exclusion Criteria only for the Participants Advancing to the Cycle 2 Portion of the Study

Participants:

3.4.1 Must not have received Akynzeo® at Cycle 1.

3.4.2 Must still meet all the exclusion criteria for Cycle 1.

3.5 Source of Study Participants

3.5.1 Sample Population: Participants will be recruited at the NCORP affiliates within the URCC Research Base network. Based upon the demographics of Preliminary Study 2, which had similar eligibility requirements and was run in many of the same locations as this study is, we expect 2% of the study population to be Hispanic, and 10% to be a racial minority, mostly African-American. Since having a diagnosis of breast cancer is an eligibility criterion, we will exclude men from participating in the study because it is unlikely we could recruit enough men to conduct meaningful analyses on that participant sub-group.

3.5.2 Participants must be 18 years of age or older. Women under 18 seldom have breast cancer and it is unlikely we could recruit enough of that age group with breast cancer to conduct meaningful analyses on that participant sub-group.

Anticipated Participant Breakdown

Racial Categories	Not Hispanic or Latino: Female	Not Hispanic or Latino: Male	Hispanic or Latino: Female	Hispanic or Latino: Male	Unknown or Not Reported Female	Unknown or Not Reported Male	Total
American Indian/Alaska Native	9	0	0	0	0	0	9
Asian	49	0	0	0	2	0	51
Native Hawaiian or Other Pacific Islander	12	0	0	0	0	0	12
Black or African American	182	0	3	0	19	0	204
White	1,199	0	32	0	55	0	1,286
More Than One Race	13	0	0	0	1	0	14
Unknown or Not Reported	7	0	5	0	12	0	24
Total	1,471	0	40	0	89	0	1,600

3.6 Process of Consent

3.6.1 Prior to study initiation, the informed consent document will be reviewed and approved by the Central IRB (CIRB). Any subsequent changes to the informed consent will be approved by the CIRB prior to initiation. NCORP sites will use the CIRB-approved consent form, which can include any local boilerplate language previously approved by the CIRB.

3.6.2 All potential study participants will be given a copy of the CIRB-approved Informed consent to review. The site investigator/investigator's designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the patient decides to participate in the study, she will be asked to sign and date the informed consent document. The study agents will not be released to a patient who has not signed the informed consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

3.6.3 The site investigator/investigator's designee will also sign the consent form. The date of this signature should correspond with the date the participant signs.

3.6.4 The eligibility checklist must be signed and dated by a physician prior to registration and the initiation of any study procedures.

3.7 Recruitment and Retention Plan

3.7.1 Study personnel at participating NCORP sites with appropriate human subject

protection certification will monitor patient visit schedules and inform treating physicians when a patient is potentially eligible for a study. If the treating physician deems the study appropriate for the patient, and if the patient agrees to hear about it, the treating physician or study personnel will then explain the project to the patient and answer all questions.

3.7.2 Retention of participants will be supported by phone calls, which will be made to participants on Day 4, or just after if Day 4 is a non-work day, to remind participants to complete and mail back the questionnaires at both Cycle 1 and Cycle 2. These calls will be documented on the Telephone Contact Sheet.

4. REGISTRATION AND RANDOMIZATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (such as the Roster Update Management System [RUMS], OPEN, Rave,; acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their clinical practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol Principal Investigator (PI) on the IRB approval
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.
Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov

4.2 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

4.2.1 IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.
Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements
Additional requirements to obtain an approved site registration status include:
- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and

- Compliance with all protocol-specific requirements (PSRs).

4.2.2 **Checking Your Site's Registration Status:**

Site's registration status may be verified on the CTSU members' website.
- Click on *Regulatory* tab at the top of the screen
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Enrolling Participants (Cycle 1)

NOTE: Coordinators must complete REDCap training prior to enrolling participants.

4.3.1 This study consists of two parts with screening and some assessments occurring at baseline and Cycle 1 and the randomized portion of the study (N = 333) occurring at Cycle 2. At Cycle 1, we will consent chemotherapy naïve breast cancer patients about to begin a chemotherapy regimen that contains doxorubicin and/or cyclophosphamide and/or carboplatin and are scheduled to receive antiemetics that are recommended in the ASCO Clinical Practice Guidelines. We anticipate needing to consent approximately 1600 participants at Cycle 1 to meet our Cycle 2 target number. It should take three to four years to meet our targeted enrollment.

4.3.2 To enroll a participant who meets the eligibility criteria and who has signed the informed consent document, log on to the URCC NCORP Research Base website at http://www.urcc-ncorp.org/, enter your NCORP's username and password, choose "Register a Subject", and enter the information outlined in the next section. If you are unable to log on, contact the study email at URCC_16070@urmc.rochester.edu.

The following information will be requested:

a. NCORP name
b. NCORP component CTEP ID
c. Enrolling physician name
d. Enrolling physician CTEP Investigator ID
e. Name and telephone number of person performing assessments
f. Verification that participant has met all inclusion and exclusion criteria in Sections 3.1 and 3.3.
g. Verification that consent form has been signed
h. Participant's identification
    - First and last initials
    - Birth date (MM/DD/YYYY)
    - Gender
    - Race and Ethnicity
    - Five-digit zip code
    - Payment code
i. Date of first chemotherapy

A confirmation of registration will be emailed to the registering NCORP's administrator, and if requested, a confirmation email will be sent to the NCORP's coordinating center

NOTE: Immediately following registration, study staff must use the participant registration ID number to create a record in REDCap and complete the REDCap Participant Information form.

4.4 Randomization/Stratification (Cycle 2)

4.4.1 **Randomization**. Participants will not be randomized at Cycle 1. Randomization will occur following the assessment of CINV after Cycle 1, and a participant will be randomized for Cycle 2 only if the reported nausea at Cycle 1 was ≥ 3 (on a 1-7 scale). A computer-generated randomization schedule will be used to assign participants in equal numbers to the three study arms, with a random (50/50) block of 3 or 6. The schedule is prepared by and maintained by the URCC NCORP Research Base biostatistician.

4.4.2 **Stratification**. The three study arms are stratified by

- NCORP
- Presence of vomiting
- Whether the participant received doxorubicin at Cycle 1
- Chemotherapy setting (neo-adjuvant, adjuvant or metastatic)

4.4.3 Randomization is done exclusively through REDCap. Randomization occurs when both the Four Day Home Record and the Case Summary are entered and marked as complete iniREDCap. The following information will be requested:

- NCORP name
- Participant's study ID
- Did the participant report vomiting on the 4-Day Home Record Diary?
- Did the participant receive doxorubicin at Cycle 1?
- Chemotherapy setting (neo-adjuvant, adjuvant, or metastatic)

The three treatment arms for Cycle 2 are:

Arm 1

Agent	Day 1	Day 2	Day 3	Day 4
netupitant/palonosetron	One 300mg capsule approximately one hour prior to chemotherapy			
Dexamethasone	12mg PO 30 minutes prior to chemotherapy	8mg PO in the morning	8mg PO in the morning	8mg PO in the morning
Placebo to match prochlorperazine	One capsule with chemotherapy then q8h	One capsule q8h	One capsule q8h	One capsule q8h
Placebo to match olanzapine	One capsule with chemotherapy	One capsule in the morning	One capsule in the morning	One capsule in the morning

Arm 2

Agent	Day 1	Day 2	Day 3	Day 4
netupitant/palonosetron	One 300mg capsule approximately one hour prior to chemotherapy			
Dexamethasone	12mg PO 30 minutes prior to chemotherapy	8mg PO in the morning	8mg PO in the morning	8mg PO in the morning
Prochlorperazine	10mg PO with chemotherapy then q8h	10mg PO q8h	10mg PO q8h	10mg PO q8h
Placebo to match olanzapine	One capsule with chemotherapy	One capsule in the morning	One capsule in the morning	One capsule in the morning

Arm 3

Agent	Day 1	Day 2	Day 3	Day 4
netupitant/palonosetron	One 300mg capsule approximately one hour prior to chemotherapy			
Dexamethasone	12mg PO 30 minutes prior to chemotherapy	8mg PO in the morning	8mg PO in the morning	8mg PO in the morning
Placebo to match prochlorperazine	One capsule with chemotherapy then q8h	One capsule q8h	One capsule q8h	One capsule q8h
Olanzapine	10mg PO with chemotherapy	10mg PO in the morning	10mg PO in the morning	10mg PO in the morning

5. RESEARCH PROTOCOL/STUDY PROCEDURES

5.1 Summary of Study Plan

The study consists of two parts with screening and assessments occurring at baseline and chemotherapy Cycle 1 and the randomized portion of the study (N = 333) occurring prior to Cycle 2. During Cycle 1, we will screen and consent chemotherapy naïve breast cancer patients about to begin a chemotherapy regimen that contains doxorubicin, and/or cyclophosphamide, and/or carboplatin. All three of the drugs are commonly given and all have at least moderate emetogenic potential. A key inclusion criterion will be that all patients must be scheduled to receive antiemetic drugs recommended in the ASCO guidelines.(1).(1) We will screen approximately 1600 patients, or more if necessary, to meet our Cycle 2 target number. The Cycle 2 portion is conducted in those participants who experience moderate or greater nausea at Cycle 1. This is a Phase III randomized, double-blinded, placebo-controlled, 3-arm study (N = 333) that builds upon our prior CINV studies and investigates optimal control of CINV in patients who experienced CINV following initial chemotherapy. A blood draw is done prior to Cycle 1 to assess biomarkers.

At Cycle 1, all rescue medications with the following exceptions will be allowed for uncontrolled chemotherapy-induced nausea and vomiting (CINV). Use of lorazepam at Cycle 1 only for the short-term relief of the symptoms of anxiety, anxiety associated with depressive symptoms, or as

a rescue medication for breakthrough CINV is allowed for a maximum of 4 days. At Cycle 1, use of metoclopramide as a rescue medication is not allowed. At Cycle 2, all rescue medications with the exception of metoclopramide and lorazepam will be allowed for uncontrolled chemotherapy-induced nausea and vomiting (CINV). We note that these two antiemetics are not allowed because benzodiazepines and anticholinergics are excluded from the protocol. We will document the type and days when prescribed rescue medications were taken.

Study Measures

[redacted]

5.2 Schedule of Activities

Evaluation/ Procedure	Registration	Prior to beginning chemo-therapy	Cycle 1 chemo-therapy evaluation	Randomization For Eligible Participants	Cycle 2 chemo-therapy evaluation[a]
Informed Consent	X				
Assess Eligibility	X				
Participant Information (REDCap new pt record)	X				
Current Prescription Medications		X			
Blood Draw for Biomarkers		X			
Study Assessments		X	X	→	X
Telephone Contact/AE Assessment[b]			X[c]	→	X

[a] Cycle 2 assessments are for randomized participants only
[b] Telephone calls are made on or close to Day 4 of Cycles 1 and 2
[c] Eligibility for randomization at Cycle 2 will be assessed during the Cycle 1 telephone contact.

5.3 Screening, Baseline and Cycle 1 Assessments

5.3.1 **Screening:** Participants will be screened, consented for study participation, registered through the URCC NCORP Research Base online participant registration system, and entered into REDCap Participant Information. Participants must be registered prior to completing any study procedures or completing any questionnaires.

[redacted]

questionnaires to take home as well as a postage-paid envelope. The participants will need to mail the Four-day Home Record as well as any other paper questionnaires that were used back to each site in the provided postage-paid envelopes.

5.3.4. The **REDCap** online survey system is licensed to the University of Rochester. The quality of psychological and behavioral data is enhanced through use of REDCap because data entry errors due to skip patterns are removed. All participants are given an ID code that is linked to their registration ID. That ID will be used when the final dataset is de-identified. This de-identified dataset will be downloaded from the REDCap server space onto a password protected server. REDCap uses encryption algorithms to protect participant data.

5.3.5 **Phone contact** between participant and research team during Cycle 1.

5.3.5.1 Participants will be told that it is very important that they speak to the designated member of the research team on or about Day 4 and should expect a call from them on Day 4, or just after if Day 4 is a non-work day.

5.3.5.2 The designated member of the research team will initiate a phone call to participants on Day 4, or just after if Day 4 is a non-work day. All reasonable efforts must be made to speak to the participant, including making multiple calls if necessary. Note: While leaving a message for the participant to call back is permissible, continued attempts to reach the participant must be made even after leaving the message. (Permission will be obtained to leave messages on a participant's voicemail before any messages are left.)

5.3.6 The call consists of the following elements:

5.3.6.1 To remind participants to complete the questionnaires and mail back the paper forms.

5.3.6.2 To ask the participant if she experienced any adverse events, and if so, to obtain relevant details regarding that event(s). Adverse events must be recorded on the Telephone Contact Sheet and reported on the Adverse Event form if required as outlined in Sections 11 & 12.

5.3.6.3 To determine if the participant is eligible for randomization at Cycle 2 by assessing the eligibility criteria in Sections 3.2 and 3.4.

5.3.6.4 If the participant is eligible, to ask the participant if she wishes to participate in the randomized portion of the study at Cycle 2. The participant's response must be recorded on the Telephone Contact Sheet.

5.4 Intervention/Study Agent

[redacted]

[redacted]

[redacted])

[redacted]

5.4.4. Obtaining Study Agent (Additional Study Drug Information in Section 8)

Study agent will be shipped from the URCC NCORP Research Base to each participating NCORP. In order for the sites to have interventions available upon enrollment, the URCC NCORP Research Base will ship study drug for each arm to each site. Kits will be shipped to the designated pharmacy, investigator, or designee, who will be responsible for the receipt of the study drug from the research base, storage, and distribution to participants. Distribution and supply will be monitored and recorded using a modified version of the standard NCI Investigational Agent Accountability Record. Study drug can be requested by emailing the study mailbox at urcc_16070@urmc.rochester.edu.

When ordering, the number of kits of each arm and the study protocol number are required. Orders will be express mailed from the research base within 2 working days unless notified otherwise.

5.4.5. Agent Disposal

Any study agent returned by participants must be recorded on the Study Agent Return REDCap form and destroyed at the NCORP site per their institution's guidelines. At the completion of this investigation, any study drug left in stock (i.e., not dispensed to a study participant) will be destroyed at the NCORP site per their institution's guidelines and recorded on the DARF.

5.5 Evaluation During the Study Intervention – Cycle 2 Assessments

The same assessments that were used following Cycle 1 will be repeated following Cycle 2. The study ends with the completion of these assessments.

5.5.1 Phone contact between participant and research team during Cycle 2.

5.5.1.1 Participants will be told to expect a call from the designated member of the research team on Day 4, or just after if Day 4 is a non-work day.

5.5.1.2 In order to maximize the likelihood of phone contact with the participant, if the research team has not heard from the participant by mid-afternoon of Day 4, a member of the research team will initiate a phone call to participants on Day 4, or just after if Day 4 is a non-work day. All reasonable efforts must be made to speak to the participant, including making multiple calls if necessary.

5.5.2 The call has the following elements,

[redacted]

5.5.2.1 To remind participants to complete the questionnaires and mail back the paper forms.

5.5.2.2 To ask about adverse events. Adverse events must be recorded on the Telephone Contact Sheet and on the Adverse Event form if required as outlined in Sections 11 & 12.

5.5.2.3 To record when and how much of the study medication was taken.

5.6 Blood Draw

5.6.2 All requisitions, blood tubes, microfuge tubes, freezer boxes, pipettes, and labels for blood draws are provided by the URCC NCORP Research Base in the form of barcoded and pre-labeled participant kits. All participant kits are study specific.

DO NOT MIX REQUISITIONS, BLOOD TUBES, MICROFUGE TUBES OR PIPETTES ACROSS PARTICIPANT BLOOD DRAW KITS EVEN IN THE SAME STUDY BECAUSE THE BARCODES AND LABELS ARE KIT SPECIFIC.

DO NOT MIX THE FREEZER BOXES, LABELS OR EXTRA SUPPLIES PROVIDED ACROSS STUDIES EVEN URCC NCORP RESEARCH BASE STUDIES BECAUSE THEY ARE STUDY SPECIFIC.

5.6.3 All study coordinators will fill in the appropriate participant information on the requisition form in each kit when it is assigned to the participant. Each NCORP is responsible for designating an individual that is certified by URCC and a lab or facility that meets the biosafety level II criteria to perform the blood draws and to handle, dispose, store and ship the blood samples appropriately.

5.6.4 Serum will be extracted from the red top tube for future studies of protein levels assessed using Multiplex and ELISA methods as appropriate. To extract the serum, the tube will first sit upright for 30 minutes at room temperature after blood collection. The tube will then be put into a centrifuge (4°C if available) and spun for 15 minutes at 1600 x g. After 15 minutes, there should be a clear separation of the serum (yellowish liquid on top) from the other cells. If this is not evident, then centrifuge for 15 additional minutes. The upper layer of serum is then gently aliquotted into the pre-labeled pink 2.0ml microfuge tubes provided in each URCC NCORP participant blood draw kit. All microfuge tubes are then placed in the pre-labeled freezer boxes provided by the URCC NCORP Research Base and the freezer box is then placed in either a -20°C freezer or a -80° C degree freezer (-80°C is preferred if available but not required) for storage until shipped to URCC NCORP Research Base. All blood samples must be shipped to URCC within 3 months of being drawn. The serum will be stored and banked for use in future research if participants have given permission.

5.6.5 One purple top EDTA tube will be prepared and stored for measurement of GSH

metabolism. The other purple top EDTA tube and the Paxgene tube will be prepared and stored for future DNA and RNA extraction, respectively. The EDTA tubes will be rocked 10 times and then placed upright in a -20° C freezer for a minimum of 24 hours. After 24 hours, the EDTA tubes can then be transferred to a -20° or -80° C freezer if available. The Paxgene tube will be rocked 10 times, stored upright for minimum of 2 hours and a maximum of 24 hours at room temp and then placed upright in a -20° C freezer for a minimum of 72 hours. After 72 hours, the Paxgene tube can be transferred to a -80° C freezer if available. After the tubes have been frozen upright for their designated time above, they can then be placed on their side in the pre-labeled freezer boxes provided by the URCC NCORP Research Base. (Storage in a -80° C freezer after 4 days is preferred if available but not required.)

5.6.6 Shipping Supplies to NCORPs and Inventory Tracking: The participating NCORP must notify the URCC NCORP Research Base that they have IRB approval and plan to participate. A starter blood drawing package, operations manual, and an initial supply of barcoded and pre-labeled blood draw kits will be shipped to the NCORP for distribution and use.

Each NCORP site will be responsible for designating someone on the research staff to be responsible for receiving the blood draw supplies and kits. The staff member will verify that the shipment contains the correct number of supplies and kits and that the supplies and kits are in good condition. The identification numbers must be verified for accuracy and recorded. The Investigational Device Accountability Record (DARF) will be used to track supplies and kits arriving from the URCC NCORP Research Base, kits given to participants, samples stored, and samples shipped to the URCC NCORP Research Base.

5.6.7 Shipping Frozen Blood Samples to URCC NCORP Research Base:

THE URCC NCORP RESEARCH BASE MUST BE NOTIFIED AND ARRANGEMENTS MADE TO RECEIVE SAMPLES AT THE URCC NCORP RESEARCH BASE 24 HOURS IN ADVANCE PRIOR TO SHIPPING ANY SAMPLES

WE WILL NOT ACCEPT PACKAGES TO BE RECEIVED ON A FRIDAY.

To arrange shipping samples, please submit a request to our lab via REDCap survey (https://redcap.urmc.rochester.edu/redcap/surveys/?s=3A3TM83ERD). Our lab will approve of a shipping date based upon availability.

Ship Samples To:
ATTN: Cancer Control
University of Rochester Medical Center
CCPL Laboratory (2-3155)
601 Elmwood Avenue
Rochester, NY 14642

Samples must be stored frozen and shipped within 3 months. Samples can be shipped sooner if storage space is limited.

The NCORPs are responsible for shipping all samples to the URCC NCORP Research Base. All samples must be shipped priority overnight and frozen on dry ice. Each NCORP is responsible for adhering to the Code of Federal Regulations guidelines when packing and shipping the frozen blood samples to the research base.

5.7 There Will Be No Follow-up Assessments

5.8 Reported Adverse Events and Potential Risks

5.8.1 The risks related to the study medication are described in Sections 8.7 – 8.10.

5.8.2 There is a chance of bruising and a very slight chance of infection with blood collection. This will be minimized through the use of standardized hospital procedures for blood collection, use of a trained phlebotomist, and sterile materials.

5.8.3 For any clinically adverse event, the toxicity grading scale established by the FDA will be used. It is as follows:

- Grade 1 toxicity (Mild): No interference with activity
- Grade 2 toxicity (Moderate): Some interference with activity not requiring medical intervention.
- Grade 3 toxicity (Severe): Prevents daily activity and requires medical intervention.
- Grade 4 toxicity (Potentially Life Threatening): ER visit or hospitalization.

5.8.4 Adverse events will be reported as per Sections 11 and 12.

5.9 Participant Withdrawal

If a study participant decides to voluntarily withdraw from the study, the study staff should ask her to clarify whether she wishes to withdraw from all components of the study or only from a single component of the study. If she requests to be withdrawn from a component of the study (e.g., study agent), research activities involving other components of the clinical trial, such as data collection activities, for which the participant previously gave consent, may continue. Any withdrawals or partial withdrawals are documented on the REDCap Withdrawal Form. Note: Completing this form is not required for participants who completed Cycle 1 of the study but did not meet the eligibility requirements to advance to the randomized portion of the study at Cycle 2.

5.10 Emergency Study Agent Disclosure

The research pharmacist at each NCORP will not know what medications each participant received. Unblinding of the study agent is ONLY permitted in the case of serious and unexpected adverse events that are definitely, probably or possibly associated with the use of the study agent AND if knowledge of the study treatment arm received is necessary for interpreting the medical event and related treatment of that medical event. Participants will not be withdrawn from the analyses should drug disclosure occur. Refer to section 8.6 for further information regarding the unblinding process.

5.11 Data & Specimen Banking for Future Research Use

[redacted]

5.12 Genetic/Genomic Research Activities

[redacted]

[redacted]

5.13 Costs to the Participant

There will be no extra cost to participants for participating in the study. All study medications will be provided at no cost to participants.

5.14 Payment for Participation

Participants will not receive remuneration for taking part in the study.

6. INTERVENTION/STUDY AGENT ADMINISTRATION AND INFORMATION

6.1 Contraindications

Because the co-administration of benzodiazepines (CNS depression) or anticholinergic medications (delirium) may cause clinically significant interactions with olanzapine(25), patients taking those medications regularly will be ineligible for the study. PRN use is allowed. The NCCN antiemetic guidelines(11) state that olanzapine should be used with caution in elderly patients, patients with dementia-related psychosis and patients with type II diabetes and hyperglycemia. As a precaution, we will therefore exclude patients with dementia-related psychosis, uncontrolled diabetes mellitus or uncontrolled hyperglycemia from participating in the study, and use caution when putting elderly patients on the study.

6.2 Current Prescription Medications

[redacted]

6.3 Dose Modification

There will be no dose modifications in this study.

6.4 Adherence/Compliance

6.4.1 All participants who provide evaluable data will be included in the analyses.

6.4.2 Compliance with taking the study medication will be assessed at the Cycle 2 phone contact.

7. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

[redacted]

7.1 Primary Endpoint

The primary outcome variable will be Average Nausea (measured on a 7-point scale anchored by "Not at all Nauseated" and "Extremely Nauseated") defined as the average nausea rating across 15 assessment points (i.e., the afternoon, evening, and night reporting periods on Day 1 and the morning, afternoon, evening, and night reporting periods on Days 2 – 4. In the event that data are missing from eleven or more of the fifteen nausea assessment points, we will set the score to missing.

7.2 Secondary Endpoints

The outcome variable for secondary aim 1 will be average nausea as described above. The outcome variable for secondary aims 2 and 3 will be Any Vomiting (yes/no).

7.3 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event, inadequate agent supply, noncompliance, concomitant medications, or medical contraindication. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events.

7.4 Off-Study Criteria

Participants may go 'off-study' for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, adverse event/serious adverse event, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdrawal of consent, death, determination of ineligibility - does not require withdrawal (including screen failure), physician request, or pregnancy.

8. STUDY AGENT/ DISTRIBUTION

8.1 Availability

All study medications provided to participants in Cycle 2 are FDA approved or commonly used for the treatment and prevention of chemotherapy-related nausea and vomiting. There are no investigational agents, but two of the medications. i.e., prochlorperazine and olanzapine will be placebo-controlled and receipt of them will be randomized. Two additional medications, i.e., Akynzeo® and dexamethasone, will be provided unblinded to all participants at Cycle 2. No medications are provided at Cycle 1.

Akynzeo® is distributed and marketed by Helsinn Therapeutics (U.S.) Inc., of Iselin, New Jersey, under license from Lugano, Switzerland-based Helsinn Healthcare S.A. Helsinn Therapeutics will provide the Investigational Drug Service (IDS) within the Department of Pharmacy at the University of Rochester Medical Center sufficient quantity of Akynzeo® to run the study. The IDS will procure the remaining study medications and will, in turn, provide all four of the study medications and matching placebo as described below to the affiliate NCORP sites.

8.2 Distribution

The study medication will only be released by the research base after IRB approval of the protocol and consent documents are received and the NCORP is approved to participate.

URCC-supplied agents must be requested by the Pharmacist, Investigator (or their authorized designees) at each NCORP. The URCC does not automatically ship agents; the site must make a request. Study drug can be requested by emailing the study mailbox at urcc_16070@urmc.rochester.edu and should include complete shipping and contact information.

8.3 Agent Accountability

The NCORP site, and responsible party designated at the site, must maintain a careful record of the inventory and disposition of all agents received from the URCC NCORP Research Base using the Investigational Agent Accountability Record (DARF). The NCORP site is required to maintain accurate records of receipt, dispensing and final disposition of study agent. Included on the DARF should be a record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number.

8.4 Packaging, Labeling and Shipping of Study Medication

[redacted]

8.5 Storage

All of the study agents should be stored at room temperature, between 68°F and 77°F (20°C and 25°C), away from heat, moisture, and light.

8.6 Blinding and Unblinding Methods

Participants, study coordinators, and investigators will be blinded to prochlorperazine/placebo group and the olanzapine/placebo group assignments. Study agents supplied to NCORPs will be labeled with a letter code that will be used to identify the assigned treatment arm for unblinding purposes. An unblinding key will be kept by IDS.

Unblinding of the study agent is ONLY permitted in the case of serious and unexpected adverse events that are definitely, probably or possibly associated with the use of the study agent AND if knowledge of the study treatment arm received is necessary for interpreting the medical event and related treatment of that medical event. In such cases, the treating M.D. or their designee can be given the treatment group assignment from the University of Rochester Investigational Drug Service. Documentation should be sent to the email address below and include participant ID number, site investigator, and reason for unblinding in the message:

Kari Gilliland
kari_gilliland@urmc.rochester.edu
585-275-1364

Participants that require emergency study agent disclosure will discontinue the study agent. The research team may continue to follow the study participant for assessment data with participant and treating physician approval.

8.7 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.9.6 Warnings and Precautions

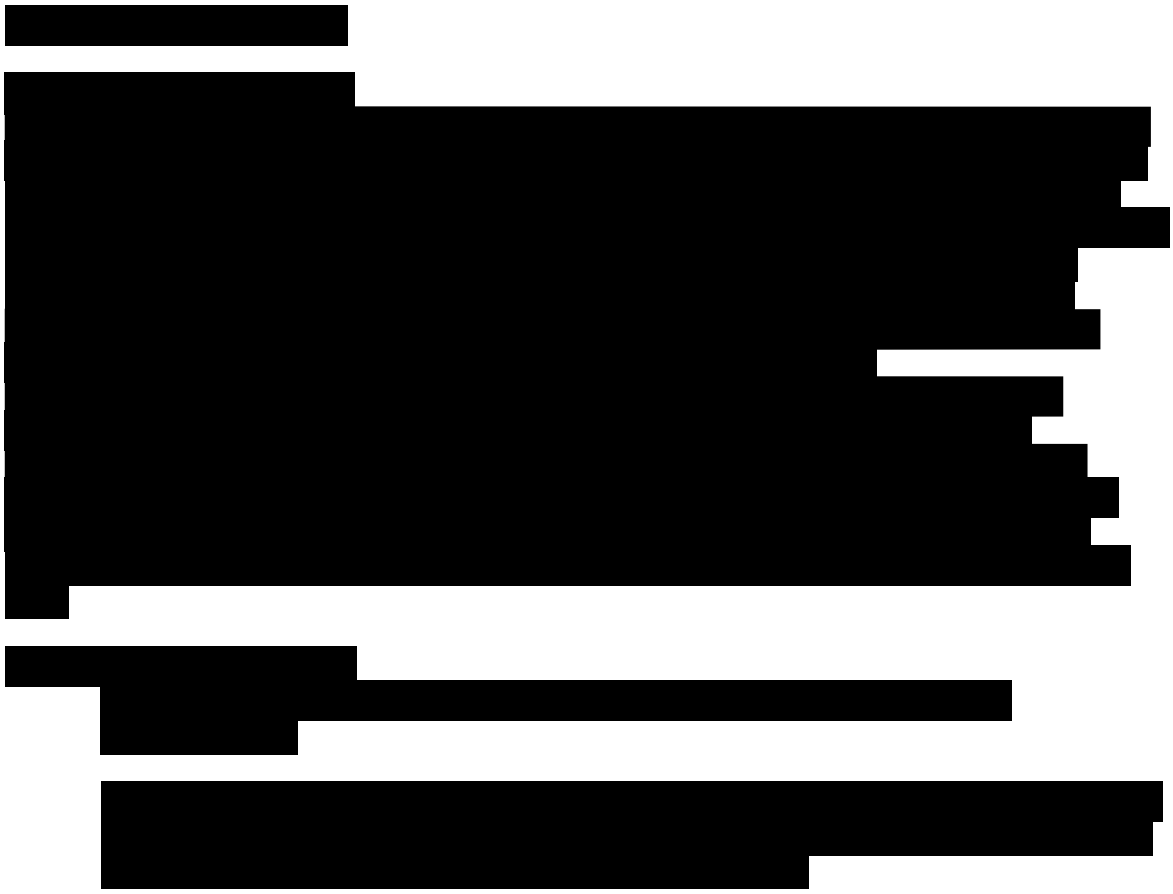
[redacted]

[redacted]

about 30% of patients.

[redacted]

).



9. CORRELATIVE/SPECIAL STUDIES

NA

10.0 SPECIMEN MANAGEMENT

10.1 Laboratories

All samples will be stored at the URMC Cancer Control and Psychoneuroimmunology Laboratory in a URCC NCORP Research Base secure and alarmed -80C freezer.

10.2 Specimen Banking

Blood samples will be stored for use in future research at the URMC Cancer Control and Psychoneuroimmunology laboratory.

10.3 Shipping Instructions

See Sections 5.6.6 and 5.6.7

10.4 Tissue Banking

NA

11.0 CYCLE 1 AE REPORTING - REPORTING ADVERSE EVENTS FOR BASELINE AND CHEMOTHERAPY CYCLE 1 PORTION OF THE STUDY.

Note: The reporting of adverse events for the Cycle 2 portion of the study, i.e., the

randomized phase at chemotherapy cycle 2 is described in Section 12 below.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized. All appropriate treatment areas should have access to the CTCAE version 5.0. The CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
The relationship to the study agent and the severity of each adverse event as judged by the investigator must be recorded. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

11.1 Any adverse event (AE) that is possibly, probably, or definitely related to the **study questionnaires or to the study blood draw** will be reported according to the guidelines below:

11.1.1 As this portion of the study is a survey with no intervention, any AE that occurs during baseline or the first chemotherapy cycle that is **not** possibly, probably, or definitely related to the **study questionnaires or to the study blood draw**, with the exception of death within 30 days, will not be reported.

11.2 Definitions

Adverse event (AE) is any untoward medical occurrence associated with the use of a medical product, which does not necessarily have a causal relationship with its use. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory test results), symptom, or disease temporally associated with the use of the study product or not considered related to the study product. The relationship of each adverse event to the study interventions must be recorded as one of the choices on the scale described below.

Attribution: An assessment of the relationship between the adverse event and study agent/intervention, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is clearly NOT related to the study questionnaires or blood draw
Unlikely	The AE is doubtfully related to study questionnaires or blood draw
Possible	The AE may be related to study questionnaires or blood draw
Probable	The AE is likely related to study questionnaires or blood draw
Definite	The AE is clearly related to study questionnaires or blood draw

Serious Adverse Event (SAE): A serious adverse event is defined as any adverse medical event (experience) that results in at least one of the outcomes listed below:

1) Death
2) Life-threatening
3) Requires inpatient hospitalization or prolongation of existing hospitalization.
4) Results in persistent or significant disability/incapacity with substantial disruption of the ability to conduct normal life functions.
5) Congenital anomaly/birth defect.
6) A medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon medical judgment, it may

jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Hospitalization (or prolongation of hospitalization): For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.

11.3 Reporting Adverse Events for Baseline and Chemotherapy Cycle 1

Note: The reporting of adverse events for the Cycle 2 portion of the study, i.e., the randomized phase at chemotherapy cycle 2 is described in Section 12 below.

All adverse events, whether observed by study staff or investigator, elicited from or volunteered by the participant that is possibly, probably, or definitely related to the **study questionnaires or to the study blood draw** should be documented. Each adverse event will include the date of onset, date of resolution, severity, and any action taken.

Recording of the adverse events will occur once the participant signs the consent form.

Adverse events will be reported to the URCC NCORP Research Base using REDCap. The following table will be utilized to report adverse events at baseline and the Cycle 1 portion of the study:

Adverse Event – for Baseline and Cycle 1 portion of the study					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated					
Unlikely					
Possible	URCC	URCC	URCC	URCC	URCC
Probable	URCC	URCC	URCC	URCC	URCC
Definite	URCC	URCC	URCC	URCC	URCC

All adverse events will be reported to the URCC NCORP Research Base via REDCap. Serious adverse events requiring expedited reporting via CTEP-AERS are described below in Section 11.4. Serious adverse events (described in section 11.2) not requiring expedited reporting through CTEP-AERS should be entered into REDCap within 10 calendar days of learning of the event.

11.4 Responsibilities for Expedited Reporting

URCC NCORP Research Base affiliates are required to notify the URCC Research Base if a participant has an adverse event requiring expedited reporting. All SAEs that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task

Attribution	Grade 4		Grade 5[b]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			CTEP-AERS[a]	CTEP-AERS[a]
Possible, Probable, Definite	CTEP-AERS[a]	CTEP-AERS[a]	CTEP-AERS[a]	CTEP-AERS[a]

[a] Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event.

[b] Includes all deaths within 30 days of the blood draw or completing the questionnaires, regardless of attribution. Any death that occurs more than 30 days after the blood draw or completing the questionnaires

and is attributed (possibly, probably or definitely) to them and is not due to cancer recurrence must be reported according to the instructions above.

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Research Base in order to complete the evaluation of the event.
For more information see:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

Contact Information for NCI Safety Reporting:

Website for submitting expedited reports	http://eapps-ctep.nci.nih.gov/ctepaers
AEMD Help Desk (for CTEP)*	301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP Trials	301-230-0159 (Back-up FAX: 301-897-7404)
AEMD Help Email:	aemd@tech-res.com
Technical (E.G., IT or computer issues ONLY) Help Phone *	1-888-283-7457 or 301-840-8202
CTEP-AERS Technical Help Email	ncictephelp@ctep.nci.nih.gov
CTCAE v 5 Help/Questions Email	ncicctcaehelp@mail.nih.gov
CTEP-AERS FAQs link	https://ctepcore.nci.nih.gov/ctepaers/help/webhelp/help%20-%20frequently%20asked%20questions.htm
CTEP-AERS Computer based training link	https://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

Office phone and fax are accessible 24 hours per day 7 days a week (The AEMD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.)

12.0 CYCLE 2 AE REPORTING - REPORTING ADVERSE EVENTS FOR THE CYCLE 2 PORTION OF THE STUDY.

Note: The reporting of adverse events for the Cycle 1 portion of the study, i.e., the survey at chemotherapy cycle 1 is described in Section 11 above.

CTCAE term (AE description) and grade: CTCAE version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to the CTCAE version 5.0. The CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
The relationship to the study agent and the severity of each adverse event as judged by the investigator must be recorded. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

12.1 Adverse event (AE) is any untoward medical occurrence associated with the use of a medical product, which does not necessarily have a causal relationship with its use. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory test results), symptom, or disease temporally associated with the use of the study product or not considered

related to the study product. The relationship of each adverse event to the study interventions must be recorded as one of the choices on the scale described below.

Attribution: An assessment of the relationship between the adverse event and study **agent/intervention**, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is clearly NOT related to the study agent (or product)/intervention
Unlikely	The AE is doubtfully related to study agent /intervention
Possible	The AE may be related to study agent/intervention
Probable	The AE is likely related to study agent/intervention
Definite	The AE is clearly related to study agent/intervention

12.2 Serious Adverse Event (SAE): A serious adverse event is defined as any adverse medical event (experience) that results in at least one of the outcomes listed below:

1) Death
2) Life-threatening
3) Requires inpatient hospitalization or prolongation of existing hospitalization.
4) Results in persistent or significant disability/incapacity with substantial disruption of the ability to conduct normal life functions.
5) Congenital anomaly/birth defect.
6) A medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon medical judgment, it may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Hospitalization (or prolongation of hospitalization): For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.

12.3 Reporting Adverse Events

Note: The reporting of adverse events for the Cycle 1 portion of the study, i.e., the survey at chemotherapy cycle 1 is described in Section 11 above.

All adverse events, whether observed by study staff or investigator, elicited from or volunteered by the participant, should be documented. Each adverse event will include the date of onset, date of resolution, severity, and the relationship to the **study agent or intervention**, and any action taken with respect to the **study agent or intervention.**

Adverse events will be reported to the URCC NCORP Research Base using REDCap. The following table will be utilized to report adverse events:

Adverse Event – for Cycle 2 portion of the study					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated			URCC	URCC	URCC
Unlikely			URCC	URCC	URCC
Possible	URCC	URCC	URCC	URCC	URCC
Probable	URCC	URCC	URCC	URCC	URCC
Definite	URCC	URCC	URCC	URCC	URCC

All adverse events will be reported to the URCC NCORP Research Base on the Adverse Event

Report Form in REDCap. Serious adverse events requiring expedited reporting via CTEP-AERS are described below in Section 12.4. Serious adverse events (described in section 12.2) not requiring expedited reporting through CTEP-AERS should be entered into REDCap within 10 calendar days of learning of the event.

*****Any rash, regardless of attribution should be reported.** See section 8.7.5***

All adverse events reported to the URCC Research Base will be reported to the Data Safety Monitoring Committee.

12.4 Responsibilities for Expedited Reporting

URCC NCORP Research Base affiliates are required to notify the URCC Research Base if a participant has an adverse event requiring expedited reporting. All SAEs that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task

Commercial reporting requirements are provided in the table below. The commercial agents used in this study are netupitant/palonosetron, olanzapine, prochlorperazine and dexamethasone.

Expedited reporting requirements for adverse events experienced by participants who have received study agent/intervention within 30 days of the last administration of commercial study agent/intervention should be reported as follow:

Attribution	Grade 4		Grade 5[b]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			CTEP-AERS[a]	CTEP-AERS[a]
Possible, Probable, Definite	CTEP-AERS[a]	CTEP-AERS[a]	CTEP-AERS[a]	CTEP-AERS[a]

[a] Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event.

[b] This includes all deaths within 30 days of the last dose of study agent with a commercial agent/intervention, regardless of attribution. Any death that occurs more than 30 days after the last dose of study commercial agent/intervention and is attributed (possibly, probably or definitely) to the agent/intervention and is not due to cancer recurrence must be reported according to the instructions above.

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Research Base in order to complete the evaluation of the event.
For more information see:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

Contact Information for NCI Safety Reporting:

Website for submitting expedited reports	http://eapps-ctep.nci.nih.gov/ctepaers
AEMD Help Desk (for CTEP)*	301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP Trials	301-230-0159 (Back-up FAX: 301-897-7404)
AEMD Help Email:	aemd@tech-res.com

Technical (E.G., IT or computer issues ONLY) Help Phone *	1-888-283-7457 or 301-840-8202
CTEP-AERS Technical Help Email	ncictephelp@ctep.nci.nih.gov
CTCAE v 5 Help/Questions Email	ncicctcaehelp@mail.nih.gov
CTEP-AERS FAQs link	https://ctepcore.nci.nih.gov/ctepaers/help/webhelp/help%20-%20frequently%20asked%20questions.htm
CTEP-AERS Computer based training link	https://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

Office phone and fax are accessible 24 hours per day 7 days a week (The AEMD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.)

Additional Instructions:

- Rash, regardless of grade or attribution should be reported.
- All pregnancies occurring in female participants during therapy or within 28 days after completion of treatment on URCC 16070 must be reported via CTEP-AERS using the event term "pregnancy, puerperium and perinatal conditions – other, pregnancy (grade 3).
- CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g., normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).
- The CTEP-AERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero to the agent used in this trial should be reported via CTEP-AERS.

13. STUDY MONITORING

13.1 Data Management Summary

This project will collect data in the following formats: paper documents, REDCap electronic questionnaires, and biospecimens (blood).

13.1.1 Paper data are entered electronically at the NCORP site as soon as they are collected by the study coordinator through the secure REDCap system, following the URCC16070 REDCap Manual available on the protocol page of the URCC NCORP Research Base website and processed as follows:

1. Paper data are visually checked by the site coordinator line by line for missing, duplicate, ambiguous or unreasonable responses and if found, they will be corrected prior to electronic data entry.
2. The coordinator will log in to the REDCap system with their uniquely assigned credentials, open the participant's record and enter the data.
3. All paper forms will be uploaded electronically to the URCC NCORP Research Base through REDCap and a copy kept on site.
4. All data entered in REDCap will be double-checked against the corresponding paper form for inconsistencies and checked for missing, ambiguous or unreasonable responses by the research base. If found, the originating site will be queried for such data.
5. One copy of the amended paper form stays on site and an electronic copy must be included in the query response sent to the URCC. Data are amended per GCP on the paper form and in REDCap, and the change is documented at the research base.
6. Queries are also generated if data are not received per the protocol timeline.
7. When all data have been received on any given case, a chart audit is performed at

the research base to ensure receipt and accuracy of all required data.

8. All paper documents are stored in locked file cabinets or in locked, limited access file rooms. The REDCap database of those documents is stored on protected servers located behind University of Rochester firewalls, with limited access.

13.1.2 REDCap data are entered electronically and processed as follows:

1. All REDCap questionnaires are directly filled out electronically by either the participant at home or the coordinator at the site.
2. Data are visually checked in the REDCap system at the URCC NCORP Research Base for ambiguous or unreasonable responses, and if found, the originating site is queried for such data.
3. When a query response is received, REDCap data are amended per GCP, and the change is documented.
4. Queries are also generated if data are not received per the protocol timeline.
5. When all data have been received on any given case, a REDCap database audit is performed to ensure receipt and accuracy of all required data.
6. The REDCap database of those electronic questionnaires is stored on protected servers located behind University of Rochester firewalls, with limited access.

13.1.3 Biospecimens: Blood kits sent from URCC have bar-coded tubes for collecting samples. One kit is used for one data collection time point of one participant. Samples are frozen on site and shipped frozen to URCC on dry ice where they are stored in locked -80^{o} freezers in a research base lab with limited access.

13.2 On-site audits are conducted at least every three years in accordance with NIH/NCI CTMB Guidelines. The primary objective of an on-site audit is to document compliance of the NCORP site with protocol and regulatory requirements, to verify accuracy of data by comparing submitted data to source documents at the NCORP site, and to provide information on good clinical practices in study conduct and data management. The equivalent of 10% of cases accrued at each component site is audited. The on-site pharmacy is also audited at that time.

13.3 Records To Be Kept

FORMS	*SCHEDULE OF DATA COLLECTION* Baseline(Pre-chemotherapy	After Chemotherapy Cycle 1	After Chemotherapy Cycle 2 for Randomized Participants Only
COMPLETED BY PARTICIPANT			
On-Study Form[1]	X		
Functional Assessment of Cancer Therapy Scale-General (FACT-G)[1]	X	X	X
Medical Symptom Checklist[1]	X	X	X
MASCC Antiemesis Tool (MAT)[1]		X	X
Four-Day Home Record (nausea, vomiting, rescue medication use, fatigue, anxiety, dizziness, and sleep disturbance)[2]		X	X
Medication Diary			X
COVID Effects	X		X
COMPLETED BY COORDINATOR			
Consent Form[3]	X		
REDCap Participant Information[4] **(must be completed immediately following registration)**	X		
Eligibility Checklist[3]	X	X(for Cycle 2)	
Blood Requisition Form[3]	X		
REDCap Current Prescription Medications[4]	X		
REDCap Case Summary Form[4]	X	X	X
Randomization		X	
Chemotherapy and Supportive Care Records (copy from medical record)[3]		X	X
Telephone Contact Sheet[3]		X	X
REDCap Adverse Event[4]	X	X	X
REDCap Investigational Agent Return Form[4]			X

[1] Paper versions of these forms are available for those participants opting out of using REDCap.
[2] Paper version only, coordinator will enter data into REDCap at the NCORP site.
[3] Paper version only, to be submitted to URCC via scanned PDF or US mail.
[4] REDCAP version only, no paper version. SAEs will be reported through CTEP-AERs per Section 11 and 12.

13.4 Data and Safety Monitoring Plan

All adverse events reported to URCC are per Sections 11 and 12.

The James P Wilmot Cancer Center Data Safety Monitoring Committee (DSMC) will serve as the DSMC of record for this study. The DSMC provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings.

Study investigators conduct continuous review of data and patient safety. The Wilmot Cancer Center Peer Review Committee has determined that progress reports of these data will be submitted annually to the DSMC for review. These reports will include: the number of participants enrolled, withdrawals, any significant toxicities, and serious adverse events both expected and unexpected. The research base maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. A copy of the AE spreadsheet is submitted with the annual progress report to the DSMC for review.

- Any adverse event that is serious, related AND unexpected must be reported within 10 calendar days from notification to the DSMC safety coordinator and DSMC chair. The NCORP sites will report to the URCC NCORP Research Base and if applicable CTEP AERS per Sections 11 and 12 of the protocol. The NCORP Research Base will be responsible for reporting to the DSMC. The DSMC Chair will determine whether further action is required, and when patient safety is of concern, may call an interim meeting.

- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the Committee for review at the annual meeting. SAE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Unless otherwise specified in the protocol, serious adverse events that require reporting (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5. See Sections 11 and 12 for specific reporting requirements for this protocol.

The Data Safety Monitoring Committee provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings. The DSMC will monitor all adverse event rates utilizing a cumulative spreadsheet listing of events submitted along with progress reports by the PI. All serious adverse events that have occurred in the prior 3 months will be reviewed at the DSMC's regularly scheduled quarterly meeting in order to confirm toxicity grade, expectedness, relatedness, sequelae, follow up required, and risk to current or future subjects.

The URCC will notify the NCORP sites immediately of any serious safety concerns identified by the DSMC. DSMC reports will be available for download on the research base website.

13.5 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. For NCI/DCP, records will be retained for at least five years after the completion of the research. The records must be accessible for inspection and copying by authorized persons of the Food and Drug Administration and the URCC Research Base.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Description

The Cycle 2 portion will be conducted in those participants who experienced moderate or greater nausea at Cycle 1. It will be a Phase III randomized, double-blinded, placebo-controlled clinical trial of an intervention examining the efficacy of the three treatment arms for control of CINV.

14.2 Data Handling

Data will be analyzed as intent-to-treat. The assumptions underlying all statistical analyses will be thoroughly checked using appropriate graphical and numerical methods.(42,43) In the case of serious violations of the assumptions, appropriate nonparametric methods or transformations will be attempted.(44,45) In the event of outlying observations, we will carefully check the data and make corrections if necessary. If no errors are found, we will conduct analyses both with and without the outlying data and report both results to assess the sensitivity. All hypothesis testing will be performed at the two-sided 0.05 level, with the exception of the Primary Analysis, which will use the 0.05/2=0.025 level. SAS, JMP and R will be used for the analyses as appropriate.

14.3 Sample Size and Power

Sample Size: The number of participants needed for the randomized portion of the study will be 111 participants per arm, or 333 total. The accrual necessary at Cycle 1 to have 333 eligible participants for the randomized portion of the trial at Cycle 2 will be1600. These numbers are derived based upon data from Preliminary Study 2. In that study, 46.1% of the randomized participants reported Peak Nausea of ≥ 3, the nausea eligibility criterion for this study. Using that number, in order to have 333 eligible participants at Cycle 2, we will need to accrue 724 participants at Cycle 1. We conservatively assume that 10% of the Cycle 1 participants who would be eligible for the randomized portion of the study at Cycle 2 will decide not to continue with the study, so we will increase our targeted accrual at Cycle 1 by 10% to 796 participants. We rounded this number to 800 for our projected recruitment at Cycle 1 and will recruit additional participants beyond the projected 800, if necessary, to reach our Cycle 2 target of 333 randomized participants. In summary, we anticipate approximately 28% of patients screened during Cycle 1 to enroll for the randomized portion of the study. Eligible patients willing to continue on the study, will be immediately following the assessment of CINV after Cycle 1 of chemotherapy randomized to continue on the study. Randomized portion of the study starts at Cycle 2 of chemotherapy. Following URCC Research Base standard operation procedures, data are evaluated for quality immediately upon its receipt. Moreover, the statistical group routinely performs data quality checks to identify problems so corrective action can be taken early. Therefore, we anticipate the data analysis to begin 4-6 weeks after full enrollment is completed and data has matured.

Update 04/29/2020: Based on the first 517 subject, 214 were eligible for Cycle 2 for 41.4%, falling slightly below of our preliminary estimate of 46.1%. Of the 214 subjects eligible for Cycle 2, only 135 (63%) decided to continue with the study. We had assumed a maximum of 10% would not continue with the study, while in reality 37% of subjects did not continue the study. Therefore, it is necessary to increase our Cycle 1 accrual to 1,200 subjects in order to meet our Cycle 2 target of 333 randomized participants, as the majority of our statistical assumptions are based on that sample size.

Update 08/01/2022: Based on the first 1,084 subjects, 413 were eligible for Cycle 2 for 39.0%, falling slightly below of our preliminary estimate of 41.1%. Of the 413 subjects eligible for Cycle 2, only 241 (58%) decided to continue with the study. We had assumed a maximum of 10% would not continue with the study, while in reality 42% of subjects did not continue the study. Therefore, with recruiting 1500 patients for Cycle 1, it is expected on average (probability 50%) that =333 will enroll for Cycle 2. To ensure high probability to reach the targeted goal n=333 for Cycle 2, we propose to recruit n=1600 for Cycle 1. Recruiting n=1600 patients for Cycle 1 provides 90% probability to meet our Cycle 2 target of 333 randomized participants, as the majority of our

statistical assumptions are based on that sample size.

Power: Our target accrual of evaluable participants for the randomized portion of the study is 100 participants per arm. We conservatively assume that 10% of randomized participants will fail to provide evaluable data so we will recruit 111 participants per arm, or 333 total. The standard deviation and pre-post correlation for average nausea at cycle 2 for 35 participants in an ongoing R01 examining acupressure bands in addition to standard antiemetics in breast cancer patients beginning chemotherapy who had nausea of >= 3 at cycle 1 and provided data at cycle 2 and did not use acupressure bands were 0.953 and 0.5, respectively.

For the Primary aim, we will use a one-way analysis of variance on Post – Pre change scores. We have Arms 1 (control), 2, and 3. Two tests will be done using contrasts: 1 vs. 2 and 1 vs. 3, and a significance level of 0.05 / 2 = 0.025. Using the numbers above, we estimate the SD of the change scores to be 0.953, conservatively assuming a pre-post correlation of 0.5. When the sample size in each of the 3 groups is 100, we calculate that our planned one-way analysis of variance will have 90% power to detect a difference in means of 0.48, or a half standard deviation. In light of the fact that there are no minimum clinically important difference (MCID) guidelines for changes in our average nausea measure, this can be considered to be a clinically relevant change.(46)

14.4 Calculation of the Primary Outcome Variable

The primary outcome variable will be Average Nausea (measured on a 7-point scale anchored by "Not at all Nauseated" and "Extremely Nauseated") defined as the average nausea rating across 15 assessment points (i.e., the afternoon, evening, and night reporting periods on Day 1 and the morning, afternoon, evening, and night reporting periods on Days 2 – 4. In the event that data are missing from eleven or more of the fifteen nausea assessment points, we will set the score to missing.

14.5 Primary Objectives and Analysis Plans

14.5.1 The **Primary Aim** is to determine if control of nausea at Cycle 2 in participants who experienced CINV at Cycle 1 is improved by the addition of either prochlorperazine or olanzapine to the control arm of netupitant, palonosetron and dexamethasone.

14.5.2 **Primary Hypothesis**: Control of nausea at Cycle 2 in participants who experienced CINV at Cycle 1 despite receiving ASCO-recommended antiemetics(1) can be improved by the addition of either prochlorperazine or olanzapine to the standard antiemetic combination of netupitant, palonosetron and dexamethasone.

14.5.3 **Primary Analysis**: We will use a one-way analysis of variance on Post – Pre change scores. We have Arms 1 (control), 2, and 3. Two tests will be done using contrasts: 1 vs. 2 and 1 vs. 3, using a significance level of 0.05 / 2 = 0.025.

14.6 Secondary Objectives, Endpoints, Analysis Plans

14.6.1 **Secondary Aim 1** is to determine if olanzapine is more effective than prochlorperazine in controlling nausea at Cycle 2 in participants who experienced CINV at Cycle 1 when used in combination with netupitant, palonosetron and dexamethasone. This will be assessed by estimating the contrast D = (3 – 1) – (2 – 1), where 3 is the Arm 3 mean, 2 is the Arm 2 mean, and 1 is the Control mean, and testing whether D = 0 versus the one-sided alternative hypothesis that D > 0.

14.6.2 **Secondary Aims 2 and 3** will compare the effects of the interventions on vomiting

by fitting a generalized linear model. The response will be Any Vomiting (yes/no) after Cycle 2, treatment arm as the main factor, and Any Vomiting after Cycle 1 as a covariate. Estimation will be performed using maximum likelihood assuming a binomial distribution and logit link. The same group of contrasts described in the Primary Aim analysis will be estimated and tested, with a significance level of 0.025 to adjust for multiple tests.

14.7 Exploratory Analyses:

14.7.1 We will create an empirically-based algorithm predicting nausea from breast cancer chemotherapy regimens. To do so, we will use the Cycle 1 diary data (total N = approximately 1600 overall) to develop a predictive model for the risk of developing nausea, using age, race, ethnicity, QOL, alcohol consumption, susceptibility to nausea, expectancy, anxiety, level of nausea on the day prior to treatment, and prior history of nausea as potential predictors. For this analysis, the outcome will be binary, with Nausea=YES if Peak Nausea $\geq$ 3 and NO otherwise. We will apply two modeling paradigms: 1) Classification Trees, and 2) logistic regression.

14.7.1.1 Classification trees consist of finding a series of binary rules with which to base classifications, e.g., if Age is under 65, Race is Caucasian, and highly emetogenic chemotherapy agents are used, there is a X% risk of CINV. These models are very easy to apply in practice and have been shown to be especially effective if there are interactions between the predictors in the model.(47) We will use Conditional Tree methodology for the computations.(48)

14.7.1.2 Logistic regression will also be performed. This method can be superior to classification trees if there are few, if any, interactions among the predictor variables. The best model will be chosen using leave-one-out cross validation, where an observation is set aside; the model is fit to the remaining ones, and the fitted model is used to predict the set-aside observation. This is repeated for each observation. The resultant set of predictions is compared to the observed data in terms of misclassification rate, sensitivity, specificity and area under the curve.

14.7.2 We will compare the effects of the interventions on QOL, as assessed by the FACT-G, by following the same procedures described under the Primary Aim and the first Secondary Aim, using change in the FACT-G scores as the response.

14.7.3 Descriptive analyses will be conducted on the frequency and severity of side-effects, i.e., sleep disturbance, fatigue, anxiety, and dizziness, across treatment conditions.

14.7.4 Assessment of biological factors (e.g. GSH recycling, genetic markers) may help identify a subgroup of patients at high risk for development of cancer-related or treatment-related side effects, or response to treatment. Assays to investigate these factors may include, for example, measurement of GSH metabolism, assessment of genetic variants such as SNPs, measurement of cytokines, or measurement of proteins associated with drug absorption, distribution, metabolism, and excretion. The most promising assay(s) will be selected at the time of analysis based on the current state of the science.

14.8 Interim Analysis

There will be no interim analysis for this protocol.

14.9 Ancillary Studies

Ancillary studies could include secondary data analyses and use of blood samples for future research.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the NCORPs must obtain written approval to conduct the study from the NCI Central IRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the CIRB prior to implementation of any changes.

After the study is closed to accrual, it should not be permanently closed at the community sites until notified to do so by the URCC NCORP Research Base.

15.2 Submission of Regulatory Documents

All regulatory documents are reviewed at the NCORP for completeness and accuracy prior to submission to URCC. Once review is completed by the NCORP, the original regulatory documents are forwarded to the URCC Regulatory Compliance Specialist as follows:

URCC_Regulatory@urmc.rochester.edu

15.3 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice, and the applicable regulatory requirements.

16. FINANCING, EXPENSES, AND/OR INSURANCE

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