Official Title: Netupitant/Palonosetron Hydrochloride and Dexamethasone With or Without Prochlorperazine or Olanzapine in Improving Chemotherapy-Induced Nausea and Vomiting in Patients With Breast Cancer

NCT Number: NCT03367572

Document Date: 01/04/2023

Study Title for Study Participants: Testing the Addition of Two Approved Drugs, Olanzapine or Prochlorperazine, for Persistent Nausea

Official Study Title for Internet Search on http://www.clinicaltrials.gov:

URCC-16070: Treatment of Refractory Nausea (NCT03367572)

This consent form describes a research study, what you may expect if you decide to take part and important information to help you make your decision. Please read this form carefully.

The study staff will explain this study to you. Please ask questions about anything that is not clear before you agree to participate. You may take this consent form home to think about this study and discuss with family or friends.

- Being in this study is voluntary – it is your choice.
- If you join this study, you can change your mind and stop at any time.
- There are risks from participating and you should understand what these mean for you.

The study is being conducted by the University of Rochester Cancer Center (URCC) and its affiliates throughout the United States in the National Cancer Institute Community Oncology Research Program.

What is the usual approach to controlling chemotherapy-related nausea and vomiting?
Antiemetics are drugs that are used to prevent or lessen nausea and vomiting. There are approved and well-established guidelines for the use of antiemetic regimens. Despite these guidelines and the great improvements in managing nausea and vomiting made during the last 25 years, some patients will still experience chemotherapy-related nausea and vomiting. You are being asked to participate in this study because you are about to begin chemotherapy for breast cancer and are scheduled to receive an antiemetic regimen that is in accordance with the American Society of Clinical Oncology guidelines. One side effect of chemotherapy may be chemotherapy-related nausea and vomiting.

What are my other choices if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- You may choose to receive usual care by your doctor as described above
- You may choose to take part in a different study, if one is available

Why is this study being done?
The purpose of this study is to see if adding either prochlorperazine or olanzapine to the standard antiemetic regimen of Akynzeo and dexamethasone at chemotherapy cycle 2 can improve chemotherapy-related nausea and vomiting in people who experienced it at chemotherapy cycle 1. We also want to find out if either of these drugs is more effective than the other in controlling chemotherapy-related nausea and vomiting. In this study you will get the standard antiemetic regimen of Akynzeo and dexamethasone. Additionally, you will get either prochlorperazine or olanzapine or a placebo. Prochlorperazine and olanzapine are drugs that are commonly used for nausea and vomiting. A placebo is lactose filled capsule made to look exactly like the prochlorperazine and olanzapine capsules, but has no active medication in it.

The study consists of two parts. **Part 1** occurs at the first chemotherapy cycle and is a survey of approximately 1600 patients to help us determine what factors are related to the occurrence of chemotherapy-related nausea and vomiting. The factors we will assess are: age, race, ethnicity, current quality of life, alcohol consumption, education, susceptibility to nausea, expectancy for the development of chemotherapy-related nausea and vomiting, anxiety, level of nausea on the day prior to treatment, and prior history of nausea. We are also collecting blood prior to your first chemotherapy to assess possible biomarkers of chemotherapy-related side effects. These biomarkers include genetic factors as well as levels of glutathione. Glutathione is an antioxidant found in most cells of the human body and a small prior study found a link between glutathione recycling and chemotherapy-related nausea and vomiting.

Approximately 1600 people will take part in this portion of the study with about 333 of these patients going on to part 2. We expect that between 1/3 and 1/2 of these 1600 patients will have chemotherapy-related nausea. It is only these patients who experienced chemotherapy-related nausea who will participate in Part 2 of the study.

Part 2 of the study occurs at the second chemotherapy cycle and will include only patients who experienced moderate or greater nausea at Cycle 1. The purposes of Part 2 are to:

(1) Compare any effects of adding olanzapine to a standard, approved antiemetic regimen for reducing nausea and vomiting

(2) Compare any effects of adding prochlorperazine to a standard, approved antiemetic regimen for reducing nausea and vomiting.

There will be about 333 people taking part in this portion of the study.

What are the study groups (Arms) in Part 2?
Part 2 of the study has three study groups. The three study groups are described below and also shown in the figure on the next page. All patients in all three study groups will receive a standard, approved antiemetic regimen consisting of Akynzeo® and dexamethasone.

Additionally:

- Arm 1 will receive 4 placebo capsules per day for four days. Three of these four placebo capsules will match prochlorperazine and one will match olanzapine.

- Arm 2 will receive prochlorperazine capsules three times per day for four days as well as 1 placebo capsule per day for four days. This placebo capsule matches the olanzapine capsule

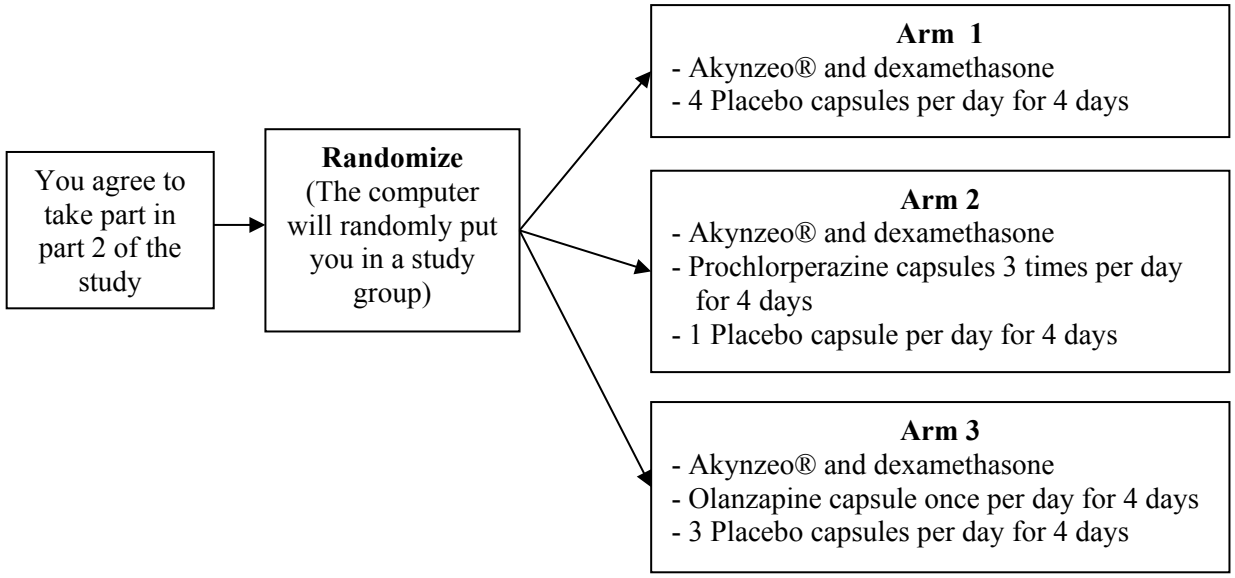
- Arm 3 will receive an olanzapine capsule once per day for four days as well as 3 placebo capsules per day for four days. These placebo capsules match the prochlorperazine capsules.

All study medications will be taken by mouth. All study medications are FDA approved or commonly used for the treatment and prevention of chemotherapy-related nausea and vomiting.

The effects of adding olanzapine or prochlorperazine will be compared to each other and to placebo. A placebo is a capsule that looks like the study drug but contains no medication. Either of these different approaches could reduce nausea but could also cause side effects.

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the others. Neither you nor your physician will know which arm you have been assigned to. This is called double-blinding.

The figure below shows the three study groups (Arms) and how you will be randomly assigned to one of those three groups.



How long will I be in this study?
Part 1 of the study will last four days beginning with the day you receive your first chemotherapy. If you participate in Part 2, you will receive the study medication for four days beginning with the day you receive your second chemotherapy. After you finish the study medication, your doctor will continue to watch you for side effects and follow your condition for 30 days.

What extra tests and procedures will I have if I take part in this study?
Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there is one extra blood draw that you will need to have if you take part in this study.

Prior to First Chemotherapy Assessment for All Participants

- **Blood draw:** Approximately 35ml (about two tablespoons) of blood will be taken prior to your first chemotherapy. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. It will be used to measure genetic factors and levels of glutathione that may be associated with chemotherapy-related side effects. Leftover blood samples collected for the current study will be used in other analyses as appropriate. This will be discussed in the section of this

consent form on optional studies. Your privacy is very important and the researchers will make every effort to protect it. Your blood sample will stored in locked and alarmed freezers within University of Rochester Medical Center Cancer Control and Psychoneuroimmunology Laboratory, which are accessible by limited research staff with electronic card swipe and key. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. The results will not be available to you or your doctor. Neither you nor your health care plan/insurance carrier will be billed for this blood draw.

- **Questionnaires:** Complete questionnaires that ask basic information about your medical history, current medication usage, quality of life, current nausea and vomiting, and current medical symptoms. You will complete questionnaires either electronically on a computer or on paper. If you choose to complete questionnaires electronically, research staff will collect your email address so you can receive, by email, the link to complete the questionnaires. You have the option to not provide your email address and complete questionnaires on paper. These forms will take approximately 15 minutes to complete.
- **Pregnancy Status**: We will confirm that you are not pregnant prior to going on the study by reviewing your medical record.
- We will review your medical record to identify information about your cancer and treatments.

Assessment Following the First Chemotherapy for **All Participants**

- **Questionnaires:** Complete questionnaires that ask about quality of life, nausea and vomiting, and medical symptoms during the 4-day period following your chemotherapy. These forms will take approximately 15 minutes to complete.
- Research staff will call you on the fourth day after your chemotherapy to remind you to complete the questionnaires and to assess your eligibility to participate in Part 2 of the study. A maximum of three attempts to reach you will be made. You will be asked to provide permission to leave messages on your voice mail.

Please circle your answer to show whether or not you give permission for messages to be left on your voice mail:

YES NO

Assessment Following the Second Chemotherapy for **Participants in Part 2 Only**

- **Questionnaires:** Complete questionnaires that ask about quality of life, nausea and vomiting, and medical symptoms during the 4-day period following your chemotherapy. These forms will take approximately 15 minutes to complete.
- Research staff will call you on the third day after your chemotherapy to remind you to complete the questionnaires and ask if you took the study medication. A maximum of two attempts to reach you will be made.

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

If you choose to take part in this study, there is a risk that:

- Bruising, bleeding, pain and infection may occur where the blood sample is taken.
- The study drugs may not be better, and could possibly be worse, than the usual approach.

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

There is also a risk that you could have side effects from the study drugs.
Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

All four of the medications provided in this study are standard, approved drugs for preventing and treating chemotherapy-related nausea and vomiting or commonly used for this purpose. Two of these medications, Akynzeo® and dexamethasone, are provided to all patients and are not being studied in in this protocol per-se. They are included because they or their equivalents are provided to most patients receiving the chemotherapy regimen you are scheduled to receive.

Olanzapine and prochlorperazine are the two drugs being studied in this research. While these are also drugs commonly used for preventing and treating chemotherapy-related nausea and vomiting, they are not typically added to the combination of Akynzeo® and dexamethasone. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you

The tables below show the most common and the most serious side effects that researchers know about all four drugs used in this study:

Akynzeo® (Netupitant/palonosetron):

Netupitant/palonosetron (Akynzeo®) was approved by the U.S. Food and Drug Administration to treat nausea and vomiting in patients undergoing cancer chemotherapy in October 2014.

Possible side effects of netupitant/palonosetron include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving netupitant/palonosetron, 3 or more may have:	
• Belly pain, feeling uncomfortably full after eating • Fatigue • Constipation	• Physical weakness or lack of energy • Headache • Patches of red skin

Possible side effects of dexamethasone include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, more than 20 and up to 100 may have:	
• High blood pressure which may cause headaches, dizziness • Skin changes, rash, acne • Swelling of the body, tiredness, bruising • Weight gain in belly, face, back and shoulders • Pain in belly • Damage to the bone which may cause joint pain or loss of motion	• Bleeding of the eye • Infection • Glaucoma • Difficulty sleeping • Mood swings • Diabetes • Increased appetite and weight gain • Loss of bone tissue

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, from 4 to 20 may have:	
• Cloudiness of the eye, visual disturbances • Non-healing wound	• Heartburn • Kidney stones

RARE AND SERIOUS In 100 people receiving dexamethasone, 3 or fewer may have:	
• Blurred vision • Bleeding from sores in stomach	• Broken bones

Possible side effects of prochlorperazine include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving prochlorperazine, from 1 to 30 may have	
• Drowsiness • Dizziness • Blurred vision	• Skin reactions • Low blood pressure • Low white blood cell count

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving prochlorperazine, from 1 to 10 may have:	
• Infection • Secretion of breast milk • Absence of menstrual period • Tremor or shakiness • Constipation	• Too much bile in the blood causing yellow skin, gums, eyes Feeling restless • Abnormal movements of face muscles and tongue

RARE AND SERIOUS In 100 people receiving prochlorperazine, 1 or fewer may have:	
• Involuntary jerking of muscles • Fever • Muscle rigidity • Irregular heartbeat	• Sudden death • Swelling of tissues • Bluish discoloration of the skin • Blood clots

Olanzapine:
Patients taking olanzapine-containing products who develop a fever with a rash and swollen lymph glands, or swelling in the face, should seek medical care right away.

Possible side effects of olanzapine include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving olanzapine, five or more may have:	
• Hyperglycemia, also known as high blood sugar • Falls • Swelling of tissues • Abnormal gait • Not able to control bladder	• Fever • Sleepiness • Pneumonia • Dry mouth • Visual hallucinations

RARE AND SERIOUS In 100 people receiving olanzapine, 1 or fewer may have:	
• Seizures • Back or chest pain • Swelling or pain in arms or legs • Accidental injury • Bruising • Vomiting • Increased appetite • Weight gain	• Shakiness • Stiffness • Difficulty saying words • Inflammation of the nose • Cough, sore throat • Vision problems • Not able to control bladder • Urinary tract infection

Questionnaires:

Although very unlikely, it is possible that answering some of the questions may cause you to feel upset or worried. You do not have to answer any questions that make you uncomfortable.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant or breastfeed while in this study. The study medications used in this study could be very damaging to an unborn or nursing baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. Tell your study doctor right away if you think you may have become pregnant during this study or within 28 days or your last dose of study medication.

What possible benefits can I expect from taking part in this study?
It is not possible to know at this time if the addition of either olanzapine or prochlorperazine to a standard antiemetic regimen is better than the usual approach, so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?
Yes, you can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible, so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

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

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

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

What are the costs of taking part in this study?
The study medication for those patients participating in Part 2 of the study at Cycle 2 is provided at no charge. The cost of getting the study medication ready and giving it to you is also provided at no charge.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.
You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?
If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.
If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?
Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

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

- The University of Rochester and its affiliates in the NCI Community Oncology Research Program
- The NCI Central Institutional Review Board, which is a group of people who review the research with the goal of protecting the people who take part in the study
- James P. Wilmot Cancer Center Data Safety Monitoring Committee
- The Department of Health and Human Services
- The Food and Drug Administration and the National Cancer Institute

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

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

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

OPTIONAL STORAGE OF ANY LEFTOVER BLOOD FOR FUTURE LABORATORY STUDIES

Please note that this storing of leftover blood does not involve an additional blood draw. It is only for the storing of any remaining blood after the analyses for the current study are completed.

Researchers are trying to learn more about chemotherapy-related side effects. Much of this research is done using blood samples or tissue. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.
Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, the researchers will store and use any leftover blood from your sample as well as your related health information for medical research to learn about, prevent and treat chemotherapy-related side effects. These blood samples will not be made available for use by investigators outside of the URCC Research Base unless there is a collaborative agreement with the study's lead investigator. We will not be able to diagnose you with any disease. The DNA analyses are only for information-gathering purposes and are not known to put you at risk for any disease. These are not clinical laboratory tests, only research tests and results will not be given to you or your doctor and will not be put in your medical record. The research that may be done is unknown at this time.

WHAT IS INVOLVED IN STORING MY BLOOD SAMPLE?

If you agree to take part, here is what will happen next:
1) Your left over blood sample and some related health information will be stored in a storage facility at the Cancer Control and Psychoneuroimmunology Laboratory at the University of Rochester and supported by the National Cancer Institute.
2) Your left over sample will be stored with samples and information from other people who take part in this study. The samples will be kept until they are used up.
3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.

WHAT ARE THE POSSIBLE RISKS OF STORING MY BLOOD SAMPLE?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?
Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any staff with access to the list must sign an agreement to keep your identity confidential.
3) Information that identifies you will not be given to anyone, unless required by law.
4) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?
You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?
There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND ABOUT STORING MY LEFTOVER BLOOD?
If you decide you no longer want your sample to be used, you can call the study doctor who will let the researchers know. Then, any sample that remains in storage at the University of Rochester will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?
If you have questions about the use of your samples for research, contact the study doctor _____ (insert name of study doctor[s]) at _____ (insert telephone number).

<u>Please circle your answer to show whether or not you would like to take part:</u>
Leftover blood from my sample and related information may be kept for use in future health research.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

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

_____	_____
Participant's signature	Date of signature
_____	_____
Signature of person conducting informed consent discussion	Date of signature