MC18C3 / 18-009108

Phase II Trial of Rifaximin in Patients With Early Stage HER2 Positive Breast Cancer With Gastrointestinal Toxicities Related to Pertuzumab-Based Therapy

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MAYO CLINIC

Name and Clinic Number

Approval Date: **December 29, 2021**
Not to be used after: **December 28, 2022**

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC18C3: Phase II trial of Rifaximin in patients with early stage HER2 positive breast cancer with gastrointestinal toxicities related to pertuzumab-based therapy

IRB#: 18-009108

Principal Investigator: Dr. Saranya Chumsri and Colleagues

Key Study Information

This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. **Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision.** You should not sign this form if you have any questions that have not been answered.	
It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits or rights you would normally have if you choose not to take part.
Research Purpose	The purpose of this research is to study the effectiveness of rifaximin to reduce the incidence and severity of pertuzumab induced gastrointestinal toxicities (PIGT) without interrupting or delaying your chemotherapy schedule which may negatively impact your cancer outcome. You have been asked to take part in this research because you are in the early stages of HER2 Positive breast cancer and are being treated with a pertuzumab-based chemotherapy as part of your standard of care.
What's Involved	Study participation involves: • Standard of care based treatment (Pertuzumab-based chemotherapy) • Blood tests

	• Physical exams • Questionnaires • Treatment of Pertuzumab Induced Gastric Toxicities (PIGT) if they occur during the first cycle of treatment using rifaximin • Optional Hydrogen Breath Test • Optional Research Urine Sample • Research Stool collection • Patient Medication Diary
Key Information	You must be willing to provide mandatory stool samples for the study. We will ask you to fill out questionnaires about your stool and gastric symptoms. The questionnaires will take about 5-15 minutes to complete. You will be in the study for about 6 months. Salix Pharmaceuticals, Inc. is funding the study. Salix Pharmaceuticals, Inc. will pay the institution to cover costs related to running the study. You may not benefit from taking part in this research study. It is for the benefit of research. You don't have to be in this study to receive treatment for your condition. Talk to the Principal Investigator or your doctor if you have any questions about any of these treatments. Possible risks may include drug to drug interaction with rifaximin. If you are receiving warfarin, the study doctor will monitor you carefully and make dose adjustments, if necessary.
Learn More	If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.

Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you either a printed or electronic copy of this form to keep. A copy of this form will be put in your medical record.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

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Contact Information

If you have questions about …	You can contact …
▪ Study tests and procedures ▪ Materials you receive ▪ Research-related appointments ▪ Research-related concern or complaint ▪ Research-related injuries or emergencies ▪ Withdrawing from the research study	**Principal Investigator:** Dr. Saranya Chumsri **Phone:** (904) 953-2000 **Institution Name and Address:** Mayo Clinic Florida 4500 San Pablo Rd Jacksonville, FL 32224
▪ Rights of a research participant	**Mayo Clinic Institutional Review Board (IRB)** **Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681
▪ Rights of a research participant ▪ Any research-related concern or complaint ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study	**Research Subject Advocate (RSA)** **(The RSA is independent of the Study Team)** **Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu
▪ Billing or insurance related to this research study	**Patient Account Services** **Toll-Free:** (844) 217-9591

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

A description of this clinical trial will be available on http://www.mayoclinic.org. This Web site will not include information that can identify you. You can search this Web site at any time.

Why are you being asked to take part in this research study?

You are being asked to take part in this research because you are in the early stages of HER2 Positive breast cancer and are being treated with a pertuzumab-based chemotherapy.

Why is this research study being done?

The purpose of this research is to study the effectiveness of rifaximin to reduce the incidence and severity of pertuzumab induced gastrointestinal toxicities (PIGT) without interrupting or delaying your chemotherapy schedule which may negatively impact your cancer outcome.

PIGT are common side effects from treatment with pertuzumab. Gastric toxicities appear to increase in patients on a pertuzumab-based chemotherapy. Currently, the medications that are used to treat PIGT mainly focus on relieving symptoms of PIGT, but do not remove the toxicity which causes the issue to persist. There are no other drugs approved for the treatment of PIGT.

Rifaximin has been approved by the U.S. Food and Drug Administration (FDA), but not for PIGT. If you experience PIGT, you will receive rifaximin which is still experimental; however, the FDA has allowed the use of this drug in this research study. We don't know all the ways that this drug may affect people. This study may not help you, but we hope the information from this study will help us develop a better treatment for PIGT in the future.

Information you should know

Who is Funding the Study?
Salix Pharmaceuticals, Inc. is funding the study. Salix Pharmaceuticals, Inc. will pay the institution to cover costs related to running the study.

Information Regarding Conflict of Interest:
Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her responsibilities for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study.

How long will you be in this research study?

You will be in the study for about 6 months.

What will happen to you while you are in this research study?

If you agree to be in the study, you will be asked to participate in the following:

Pre-Screening
During this visit, we will do some tests and procedures to see if you are eligible to take part in this research study. The Principal Investigator will review the results of these tests and procedures. If you aren't eligible, the Principal Investigator will tell you why. At this visit we will:

- Ask you about your medical history
- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw a blood sample
- Test your blood for pregnancy if you are a female able to become pregnant
- Start the first cycle of your standard of care, pertuzumab-based chemotherapy
- Give you a questionnaire and stool diary to fill out asking about your gastric symptoms and bowel movements. In order to participate in this study, you must agree to provide responses to these questions. The reason for this is to evaluate your gastric symptoms and to record any changes during your participation in this study.
    - 4 Point Likert Scale Questionnaire – measures the severity of your gastric symptoms using none, mild, moderate, or severe. You will complete this form on Day 1 of each pertuzumab-based chemotherapy cycle.

  - Daily bowel movement diary using the Bristol Stool Scale – Record daily bowel movement, consistency of stool, and ease of passage. You will complete the diary on Day 1 of your first cycle of pertuzumab-based chemotherapy and continue on days 2-14 after your first cycle of pertuzumab-based chemotherapy.
    You will repeat this on days 1-14 of each cycle. The study staff will collect these questionnaires from you when you return on Day 1 of each subsequent cycle.
- (Optional) Hydrogen Breath Test – test that uses the measurement of hydrogen in the breath to diagnose conditions caused by gastric symptoms. This test is optional. You can choose not to participate in the hydrogen breath test and remain in the study.
- Research Stool collection. You will be asked to provide stool samples for this study. The stool sample will be tested to analyze changes in your stool while you are in this study using fecal microbiome testing. A fecal microbiome test is conducted by analyzing the RNA in your stool to determine how much bacteria is present. You will be given a stool collection kit to store and ship your sample to Mayo Clinic. Your kit will include instruction materials, 2 capped stool collection containers, and a plastic holder to hold the collection container in the toilet.
- (Optional) Research urine collection. If you choose to participate in the research urine collection, your urine will be used to analyze your intestine's absorption ability, also known as an intestinal permeability assessment. The intestinal permeability assessment requires you to drink a premeasured amount of lactulose and mannitol and provide a urine sample. Tell your study doctor if you have an abnormally high glucose level; this will interfere with testing. All patients will be required to fast for a minimum of 6 hours, unless otherwise approved by principal investigator. You will also need to avoid artificial sweeteners for 2 days prior to test, aspirin within a week of test, and oral corticosteroids within 6 weeks of the test. You can choose not to participate in the research urine collection and remain in the study.

Study Treatment

If you are eligible to participate in this study, you will complete a maximum of 5 cycles for the purpose of this study. Each cycle is 21 days. The study is divided into 2 patient arms:

- Arm 1- You will be assigned to this arm if your doctor confirms you have experienced a PIGT after receiving your first standard of care cycle of pertuzumab-based chemotherapy. You will take a rifaximin 550 mg tablet (2 times a day) during cycles 2-6 on days 1-5 of each cycle while continuing your pertuzumab-based chemotherapy.
- Arm 2- If you do not experience PIGT, you will continue your pertuzumab-based chemotherapy per your standard of care treatment. You will not receive rifaximin.

Your study doctor will decide which treatment Arm you will be assigned for the study. During the study, you will participate in the following study visits no matter which arm you are assigned to:

Cycle 1, Day 1

- Medical history
- Physical exam
- Draw blood sample
- Questionnaires
- (Optional) Hydrogen Breath Test
- Research Stool collection
- Research urine collection

Cycle 1, Day 7-14

- Questionnaires
- (Optional) Hydrogen Breath Test
- Research Stool collection
- (Optional) Research Urine sample

Cycle 2-5, Day 1

- Medical history
- Physical exam
- Draw blood sample
- Questionnaires
- Research Stool collection
- Patient Medication Diary

End of Treatment (21 Days after last dose of pertuzumab-based chemotherapy)

- Medical history
- Physical exam
- Draw blood sample
- Questionnaires
- (Optional) Hydrogen Breath Test
- Research Stool collection
- (Optional) Research Urine Sample

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Optional Hydrogen Breath Test:
The hydrogen breath test is optional. You may choose not to participate in the hydrogen breath test and remain in the study. If you choose to participate, you may withdraw your consent at any time.

Please read the following statement and mark your choice:
I consent to participate in the Optional Hydrogen Breath Test.

☐ Yes ☐ No Please initial here: _____Date: _____

Optional Research Urine Sample:
The research urine sample is optional. You may choose not to participate in the research urine sample and remain in the study. If you choose to participate, you may withdraw your consent at any time.

Please read the following statement and mark your choice:
I consent to participate in the Optional Research Urine Sample.

☐ Yes ☐ No Please initial here: _____Date: _____

Patient Medication Diary
You will be given a patient medication diary based on your treatment Arm to record your daily study medication intake. Please complete the diary on a daily basis. Instructions on how to complete the diary will be included. The study staff will collect your medication diary on Day 1 of each cycle starting on Cycle 2. Your last entry will be collected at your End of Treatment visit.

Research Results
Tests done only for research purposes are not meant to provide clinical information or help care for you. The results are only important for research. Therefore, the results of tests done with your information and samples will not be provided to you. In the rare event that a finding might affect the health of you or your family, we will contact you and you can choose whether to receive or refuse the information. If you decide to follow up and further medical testing or care is needed, the costs will be billed to you or your insurance.

What are the possible risks or discomforts from being in this research study?

Risks associated with rifaximin

Likely risks of rifaximin ***(events occurring greater than 10% of the time)***

- Peripheral Edema (swelling)
- Dizziness, fatigue
- Ascites (Abdominal swelling)
- Nausea

Less likely risks of rifaximin ***(events occurring less than or equal to 10% of the time)***

- Headache
- Depression
- Itching of the skin (pruritus)
- Skin rash
- Abdominal pain
- Inflammation of the colon (pseudomembranous colitis)
- Anemia
- Elevated liver enzymes
- Muscle spasm
- Join pain (arthralgia)
- Increased creatinine phosphokinase (enzyme in the body)
- Viral infection of the nose and throat (nasopharyngitis)
- Shortness of breath (dyspnea)
- Nose bleed (epistaxis)
- Fever

Rare risks of rifaximin ***(events occurring less than 2% of the time)***

- Allergic reaction (anaphylaxis)
- Rapid swelling normally caused by an allergic reaction (angioedema)
- Clostridium difficile associated with diarrhea
- Scaling of the skin (exfoliative dermatitis)
- Feelings of warmth and reddening of the skin (flushing)
- Immune system reaction (hypersensitivity reaction)
- Hives (urticarial)

Rifaximin may have interactions with other drugs. For your safety during this study, call the Principal Investigator BEOFRE you take any:

- New medications prescribed by your doctor
- Other medications sold over-the-counter without prescription
- Dietary or herbal supplements

Pregnancy Risk – Fetus and Breastfeeding Infant

The effect of rifaximin on a fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these risks, women cannot take part in this study if they are pregnant or breastfeeding.

If you are a female, you must have a negative pregnancy test in order to participate in this study unless you cannot become pregnant.

Birth Control Requirements

If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

If you miss a period, or think you might be pregnant during the study, you must tell the Principal Investigator immediately.

Blood Draw Risks

The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

Stool Collection and Fecal Microbiome Risk

There are no risks associated with stool collection. However, your stool sample may contain infectious pathogens that you can spread to others. Be sure to wash your hands thoroughly with antibacterial soap after collecting your sample.

Urine Collection and Intestinal Permeability Test Risk

We cannot perform this test on diabetics with >105mg/dl fasting urine glucose concentration. If you have had allergic reactions to foods (including sugar free foods, beverages, candies, gum and mints), dietary supplements, dental products or medicines (prescription and over-the-counter)

containing sugar alcohols like sorbitol or xylitol, you should NOT take this test. It is also NOT recommended for individuals who have had allergic reactions to lactulose or are on lactose-restricted diet.

Hydrogen Breath Test Risk
There are no risks associated with the hydrogen breath test.

As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

Are there reasons you might leave this research study early?

You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator, the funding partner, Salix Pharmaceuticals, Inc. or Mayo Clinic may stop you from taking part in this study at any time:

- If it is in your best interest,
- If you don't follow the study procedures,
- If the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay.

What if you are injured from your participation in this research study?

Where to get help:
If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries?
Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. Treatment costs for research-related injuries not covered by your insurance will be paid by Mayo Clinic.

What are the possible benefits from being in this research study?

You may not benefit from taking part in this research study. It is for the benefit of research.

What alternative do you have if you choose not to participate in this research study?

You don't have to be in this study to receive treatment for your condition. Your other choices may include antidiarrheal agents such as loperamide and diphenoxylate. Talk to the Principal Investigator or your doctor if you have any questions about any of these treatments.

What tests or procedures will you need to pay for if you take part in this research study?

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Optional Hydrogen breath test
- Rifaximin (study drug)
- Research stool collection and test
- Optional Research urine collection and test
- Questionnaires

However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care.

These tests and procedures are:

- Physical exams
- Laboratory blood tests
- Pregnancy test
- Pertuzumab based chemotherapy

You will also be responsible for any co-payments and deductibles.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the "Contact Information" section of this form.

Will you be paid for taking part in this research study?

You won't be paid for taking part in this study.

There is a very small chance that some commercial value may result from the use of your sample. This could include new products like a drug or a test to diagnose a disease. If that happens, you will not be offered a share in any profits.

Will your information or samples be used for future research?

Identifiable information such as your name, Mayo Clinic number, or date of birth may be removed from your information or samples collected in this study, allowing the information or samples to be used for future research or shared with other researchers without your additional informed consent.

How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study. To protect the confidentiality of your data, a code will be used as an identifier. The code will be a registration number assigned specifically to you by the Mayo Clinic Cancer Center Registration Office.

The correlating Mayo Clinic number and your name for reference will be maintained in a secure database accessible by Mayo Clinic assigned research staff.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission (or "authorization") to Mayo Clinic.

Your health information may be collected from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Your health information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was conducted following the approved study plan, and applicable rules and regulations.

Your health information may be used and shared with:

- Mayo Clinic research staff involved in this study.
- Other Mayo Clinic staff involved in your clinical care.
- The sponsor(s) of this study and the people or groups hired by the sponsor(s) to help perform this research.
- The Mayo Clinic Institutional Review Board that oversees the research.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- A group that oversees the data (study information) and safety of this research.

How your information may be shared with others:

While taking part in this study, you will be assigned a code that is unique to you but does not include information that directly identifies you. This code will be used if your study information is sent outside of Mayo Clinic. The groups or individuals who receive your coded information will use it only for the purposes described in this consent form.

If the results of this study are made public (for example, through scientific meetings, reports or media), information that identifies you will not be used.

In addition, individuals involved in study oversight and not employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you. However, the individuals will not be allowed to record, print, copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying 'no' will not harm your relationship with your own doctors or with Mayo Clinic.

If you cancel your permission for Mayo Clinic to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

You can cancel your permission for Mayo Clinic to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
201 Building 4-60
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate at: researchsubjectadvocate@mayo.edu.

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Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission for Mayo Clinic to use and share your health information lasts until the end of this study, unless you cancel it. The study does not end until all data has been collected, checked (or audited), analyzed, and reported. Because research is an ongoing process, we cannot give you an exact date when the study will end. Sometimes this can be years after your study visits and/or activities have ended.

Enrollment and Permission Signatures

Your signature documents your permission to take part in this research.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature