MC178B / 18-000580

Phase II Study of Ibrutinib in Combination With Ixazomib in Patients With Waldenstrom Macroglobulinemia

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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: Phase II study of Ibrutinib in combination with Ixazomib (MLN9708) in patients with Waldenström Macroglobulinemia

IRB#: 18-000580

Principal Investigator: Dr. Asher Chanan-Khan and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you get at Mayo Clinic now or in the future if you choose not to participate or discontinue your participation.

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.

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 a copy of this form to keep. A copy of this form will be put in your medical record.

CONTACT INFORMATION

You can contact …	At …	If you have questions about …
MCF (Lead) Principal Investigator: Asher Chanan-Khan, M.D. **MCR Principal Investigator:** Stephen M. Ansell, M.D., Ph.D.	**Phone:** (904) 953-2000 **Institution Name and Address:** Mayo Clinic Florida 4500 San Pablo Rd Jacksonville, FL 32224 **Phone:** (507) 284-2511 **Institution Name and Address:** Mayo Clinic Rochester 200 First Street SW Rochester, MN 55905	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Mayo Clinic Institutional Review Board (IRB)	**Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681	▪ Rights of a research participant
Research Subject Advocate (The RSA is independent of the Study Team)	**Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu	▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study
Patient Account Services	**Toll-Free:** (844) 217-9591	▪ Billing or insurance related to this research study

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 https://www.mayoclinic.org/ research study website. This website will not include information that can identify you. You can search this website at any time.

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

You are being asked to take part in this research study because you were diagnosed with Waldenström Macroglobulinemia (WM) by your doctor. The plan is to have about 47 people take part in this study at Mayo Clinic.

2. Why is this research study being done?

The purpose of this research is to gather information on the safety and effectiveness of the combinational use of Ibrutinib and Ixazomib.

Ibrutinib has been approved by the U.S. Food and Drug Administration (FDA) for WM, and in this study we want to learn more about the safety and effectiveness of Ibrutinib in combination with Ixazomib.

Ixazomib (MLN9708) is still experimental and isn't approved by the U.S. Food and Drug Administration (FDA). 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. We hope the information from this study will help us develop a better treatment for WM in the future.

3. Information you should know

Who is Funding the Study?
Takeda Pharmaceuticals, Inc. is funding the study. Takeda 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.

4. How long will you be in this research study?

You will be in the study approximately 5 years or until your disease progresses.

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

Screening Period
During the screening visits, 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
- Ask you for a urine sample
- Test your [blood/urine] for pregnancy if you are a female able to become pregnant
- Bone marrow biopsy

- PET/CT imaging of your chest, abdomen, and pelvis.
- Electrocardiogram

If you agree to participate in this study, you will continue to Cycle 1. Each cycle is 28 days.

Cycle 1, Day 1
At this visit we will:
- Check your vital signs
- Ask you about side effects or health problems since your last visit
- Standard of care lab testing
- Ask you for a urine sample
- Give you a 30-day supply of the study drug, ixazomib

Cycle 1, Day 8
At this visit we will:
- Ask you about side effects or health problems since your last visit
- Standard of care lab testing

Cycle 1, Day 15
At this visit we will:
- Ask you about side effects or health problems since your last visit
- Standard of care lab testing

Cycle 1, Day 22
At this visit we will:
- Ask you about side effects or health problems since your last visit
- Standard of care lab testing

Cycles 2 and beyond, Day 1*
At this visit we will:
- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Standard of care lab testing
- Ask about side effects or health problems since your last visit
- Bone marrow biopsy, prior to cycle 7, prior to cycle 13, and if clinically indicated
- PET/CT imaging of your chest, abdomen, and pelvis. Occurs every 2 cycles, if clinically indicated.
- Electrocardiogram

- Additional blood draws for research purposes. Approximately 48mL (about 3 tablespoons) of additional blood will be drawn.
- Give you a 30-day supply of the study drug, ixazomib. You will return your empty medication bottle or unused medications.
- Return completed medication diary

***If you complete Cycle 4, you may be asked to return every other cycle until the end of your treatment. Your study doctor will determine if this option is appropriate for your care. If your study doctor feels this is not the best option for your care, you will come every cycle until the end of your treatment.**

End of Treatment
At this visit we will:

- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Standard of care lab testing
- Ask about side effects or health problems since your last visit
- Bone marrow biopsy, if clinically indicated
- PET/CT imaging of your chest, abdomen, and pelvis.
- Electrocardiogram
- Additional blood draws for research purposes. Approximately 48mL (about 3 tablespoons) of additional blood will be drawn.
- You will return your empty medication bottle or unused medications.
- Return completed medication diary

Clinical Follow-up (Occurs every 3 months after your end of treatment visit for 2 years)
At this visit we will:

- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Standard of care lab testing
- Test your [blood/urine] for pregnancy if you are a female able to become pregnant
- Ask about side effects or health problems since your last visit
- Bone marrow biopsy, if clinically indicated

- PET scan or CT scan imaging of either (or all as needed to assess your response to treatment) of your chest, abdomen, and pelvis. In some cases your doctor may recommend using an MRI to assess you disease state. The choice to select which of these tests will be made by your physician and is based on the specifics of your conditions and how best to assess your disease.
- Electrocardiogram

Study Drug Administration and Patient Medication Diary
You will receive Ixazomib (MLN9708) (4mg) to take on days 1, 8, and 15 of each cycle. You will receive Ibrutinib (420mg) to take every day for 4 weeks of each cycle. These drugs will be given to you on Day 1 of each cycle.

Ixazomib (MLN9708) should be taken on an empty stomach (either 1 hour before or 2 hours after meals) with 8 oz. of water. Swallow the capsules whole; do not open, break, or chew the capsules. If you experience a vomiting episode in the same day after taking Ixazomib, do not make up this dose. Please indicate the time you took the drug and the time you vomited in your medication dairy.

Ibrutinib should be taken with water at approximately the same time each day and can be taken with or without food. Swallow the capsules whole; do not open, break, or chew the capsules. Please avoid grapefruit, grapefruit juice, and Seville oranges during your Ibrutinib treatment. Supplements such as fish oil and vitamin E preparations should also be avoided.

During this period, we will provide you with a patient medication diary to record the dose of Ixazomib (MLN9708) and Ibrutinib you took for the day. Instructions on how to fill out the diary are included. You are to fill in the requested information on a daily basis.

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

Risks Associated with Ibrutinib

Likely risks of Ibrutinib (events occurring greater than 20% of the time)
- Diarrhea
- Fatigue
- Nausea
- Cough

- Fevers
- Anemia

Less likely risks of Ibrutinib (events occurring less than or equal to 20% of the time)

- Vomiting
- Muscle and joint pains
- Trouble swallowing
- Headache
- Constipation
- Low number of white blood cells, which are the infection fighting cells, which could put you at risks for infection
- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk for bleeding
- Decreased appetite
- Swelling of the hands and feet
- Infection of the nose, sinuses, and/or throat
- Sensation of lightheadedness or vertigo
- Shortness of breath
- Infection of the lungs
- Rash
- Back pain
- Abdominal pain
- Increase in blood pressure
- Sores in the mouth
- Common cold
- Urinary tract infection
- Skin infection
- Small red or purple spots caused by bleeding under the skin
- Nosebleed
- Inflammation of the fatty tissue underneath the skin

Rare but serious risks of Ibrutinib *(events occurring less than 2-3% of the time)*

- Generalized weakness, fatigue, and loss of strength
- Increased kidney function tests (decreased kidney function)
- Bleeding around or inside the brain
- Atrial fibrillation, an irregular heartbeat that results from the top/upper chambers of the heart “quivering” instead of beating normally

- Rapid breakdown of cancer cells which releases chemicals into the blood and may lead to reduced kidney function. Accumulation of these chemicals may harm muscle, kidney or nerve function
- Blurry vision
- Increased level of uric acid in the blood
- Dry mouth
- Dehydration
- Increase in white blood cell counts
- Low white blood cell counts with fever
- Skin redness
- Severe infection throughout the body (septic shock) including infections with Klebsiella, Parainfluenza virus, influenza, Pseudomonas, pneumocystis carinii, Staphylococcus and other
- Stomach pain
- Respiratory failure
- Acute myocardial infarction
- Cardiac arrest
- Congestive heart failure with pulmonary edema
- Circulatory collapse; is a condition in which body blood pressure decreases significantly and blood is not able to adequately flow through the body.
- Stroke (Cerebrovascular insufficiency or infarction)
- Kidney infarct (interruption of blood supply to parts of the kidney
- Splenic rupture
- Fluid around lungs
- Blood clot travelling inside blood vessels into lungs or other organs
- Generalized confusion with altered mental status
- Fractured bones
- Secondary cancers (unrelated to the Waldenstrom's macroglobulinemia)
- Deterioration of general health
- Bleeding under the skin forming a collection or clot of blood
- Destruction of the red cells
- Liver deterioration or failure
- Distention of the small bowel
- Hole in the intestines
- Bleeding into the ventricles of the brain
- Multiple organ dysfunction

- Lower pH in the blood secondary to accumulation of lactic acid
- Abnormal rapid and/or irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (Ventricular tachycardia)

Pregnancy risks of Ibrutinib
The effect of Ibrutinib on a fetus (developing baby still in the womb) is known to cause harm. It is not known whether Ibrutinib is excreted in human milk. 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.

Other Possible risks of Ibrutinib
Laboratory studies and studies in animals suggest that other side effects not seen in people so far could occur, including:

Effects on the eye

- In standard toxicity studies done in animals, a few dogs that were treated with very high doses of the study drug developed a cloudy appearance of the eye. The cause of this is unknown; however, this side effect was only seen at the highest dose tested and only in dogs not in rats. Be sure to report any eye problems that you may have to your doctor.

Bleeding effects

- In the test tube, the study drug can prevent platelets (blood clotting cells) from clumping normally. Serious bleeding has been uncommon so far with the exception of bleeding into the head and brain in patients. It is possible that treatment with the study drug could increase your chances of bruising, bleeding, bleeding from intravenous sites and bleeding during or after surgery. It is also possible that this effect could be made worse by other drugs that block platelets like aspirin, ibuprofen or naproxen or by blood thinning medicines. Tell your doctor about any prescription or over-the-counter medicines you may be taking. Patients should be off the drug for seven to ten days before an operation and should be off the drug for one week after the operation.

Second malignancies

- The risk of developing a second, unrelated cancer is considered higher for any cancer patients but this specific risk has not been determined after treatment with ibrutinib. These second cancers have been reported in patients treated with ibrutinib but it has not been determined that ibrutinib treatment specifically lead to the second cancers.

Interference with other drugs

- Some medications and some foods like grapefruit and grapefruit juice can interfere with the way your body processes the study drug. This interference could cause the levels of the study drug in your body to be too high or too low. It is possible that taking the study drug with your regular medications or supplements including vitamins may change how the study drug, your regular medications, or your regular supplements work. It is very important that you tell the study doctor about all medications or supplements you are taking during the study. If you are not completely truthful with the investigator and study staff regarding any side effects, you may harm yourself by participating in this study.

In addition to the risks listed above, there may be some unknown or infrequent and unexpected risks associated with the use of this study drug or interaction with another drug, which may be life-threatening. You will be informed of any new information, findings, or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think they are related to the study drug.

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

Risks Associated with Ixazomib (MLN9708)

Potential discomforts and risks of Ixazomib
Based on early studies of ixazomib, it is possible to predict some of the possible discomforts and risks. The data suggest that the potential risks of ixazomib are likely to be manageable if monitored and treated. However, risks could become serious and potentially life-threatening. It is possible that ixazomib may cause side effects that were not seen in animal studies or yet seen in patients. Based on early studies in patients treated with ixazomib and on studies in patients treated with Velcade (bortezomib) the following side effects might be seen:

Likely risks of Ixazomib (MLN9708) (events occurring greater than 20% of the time)

- Feeling sick to your stomach (Nausea)
- Throwing up (Vomiting)
- Loose Stool (Diarrhea)
- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk of bleeding - Thrombocytopenia)

- A low number of white blood cells, which are the infection fighting cells, which could put you at risk for infection (Neutropenia)
- A low number of a particular white blood cell, which is important to the immune system (Lymphopenia)
- Infection
- Skin rash
- Swelling of extremities
- Numbness and tingling (also known as peripheral neuropathy)
- Flu-like symptoms and other upper respiratory tract infections
- Arthralgia or joint pain
- Lung infections including pneumonia or pneumonitis
- Herpes Zoster that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time

Less likely risks of Ixazomib (events occurring less than or equal to 20% of the time)

- Decreased appetite
- Feeling tired or weak
- Abdominal pain or distension
- Back pain
- Upper respiratory tract infection
- Sensation of lightheadedness or vertigo (spinning sensation) (Dizziness)
- Blood chemical imbalance (Electrolyte imbalance)
- Excessive or abnormal loss of body fluids (Dehydration)
- Hepatic insufficiency
- Blurred vision
- Conjunctivitis
- Xerophthalmia
- Lowered red cells or anemia which may make you feel tired
- Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever
- Constipation

Rare risks of Ixazomib (events occurring less than 2-3% of the time)

- Cholestatic hepatitis
- hepatocellular hepatitis
- hepatotoxicity
- liver steatosis
- peripheral motor neuropathy

- reversible posterior leukoencephalopathy syndrome
- Stevens-Johnson syndrome
- Sweet's syndrome
- Thrombotic thrombocytopenic purpura
- Transverse myelitis
- Tumor lysis syndrome
- Thrombotic microangiopathy
- Low or high blood pressure
- A painful blistery red rash that is confined to one side of the body, similar to chicken pox (shingles or Herpes zoster)
- Effects on your nervous system that may cause painful feelings or numbness or tingling in hands and feet. The nerves that control things like your heart rate, gut movement, and urinary bladder may be affected
- Inflammatory response associated with an increase in your white blood cell count, fever, and a change in certain protein levels and chemistries in the body
- Esophageal ulcer
- Chest pain
- Abnormal liver tests
- Decreased weight
- Fainting episodes
- Decreased level of consciousness
- Tremors
- Blood clots
- Inflammation of the lungs
- Increased blood pressure in the lungs
- Nosebleeds
- Muscle weakness
- Changes in mood
- Swelling around the eyes
- Muscle aches

Rare but serious risks of Ixazomib

- Life threatening severe skin rash including severe rash that can lead to skin peeling and life threatening complications (Stevens Johnson syndrome)
- Abnormal heart rhythms
- Worsening of your heart function (Congestive heart failure)
- Inflammation or scarring of the lungs (pneumonitis or pulmonary fibrosis) that could affect the function of your lung that could be serious enough to result in death

- Liver failure
- Abnormal clotting of the blood in small blood vessels resulted from low levels of platelets and red blood cells (Thrombotic microangiopathy (TMA) including (Thrombotic Thrombocytopenic Purpura (TTP)) and Hemolytic uremic syndrome (HUS). Symptoms may include fatigue, fever, bruising, nose bleeds, and decreased urination. These disorders can occasionally be fatal. TMA, TTP, and HUS have been rarely seen (<0.1%) in patients treated with Ixazomib.
- A complication that may occur if the cancer cells die too quickly that includes inappropriate increase or decrease of various natural chemicals in the blood stream, called uric acid, phosphorus, potassium, creatinine, and calcium. Severe tumor lysis can result in kidney failure and may harm muscle or nerve function (Tumor lysis syndrome)
- High creatinine and renal failure. The amount of creatinine (a waste product made by your body) in your blood helps your doctor understand how your kidneys are working. A high creatinine level means your kidneys are having trouble working well. Patients who had lost body water because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney (dialysis).
- Obstruction of the bowels
- A condition that can be associated with abnormal neurological function and seizures (posterior reversible encephalopathy syndrome; PRES)
- Inflammation of the spinal cord (transverse myelitis)
- Progressive multifocal leukoencephalopathy, a rare condition associated with inflammation in the brain has been reported, but it is not clear if it is related to the medication

Ixazomib (MLN9708) should not be taken if you have ever had a serious allergic reaction to the active substance or any of the inactive ingredients used in its formulation.

Pregnancy risks of Ixazomib
The effect of Ixazomib (MLN9708) on a fetus (developing baby still in the womb) is known to cause harm. It is not known whether Ixazomib or its metabolites are present in human milk. 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 for female participants
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)

You must use birth control for the entire study and for at least 3 months after your last dose of the study drug.

Birth Control for male participants
If you are sexually active, and able to father a child, you must agree to use one of the birth control methods listed below:

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

You must use birth control for the entire study and for at least 3 months after your last dose of study drug.

Overdose has been reported in patients taking Ixazomib (MLN9708). Reports of accidental overdose have been associated with risks such as nausea, lung infections including aspiration pneumonia, multiple organ failure, and death. It is important to take only one dose of Ixazomib at a time, and only at the prescribed intervals.

Bone Marrow Biopsy and Aspiration
Bone marrow exams are generally safe procedures. Complications are rare but can include:

- Excessive bleeding, particularly in people with low numbers of a certain type of blood cells (platelets)
- Infection, especially in people with weakened immune systems
- Long-lasting discomfort at the biopsy site
- Penetration of the iliac (hip area) bone (and much less commonly, breastbone (sternum) during sternal aspirations), which can cause discomfort in the specific area.

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.

Your doctor will discuss the risks of the other tests and procedures as these tests and procedures are part of your standard clinical care.

7. 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, Takeda *(the sponsor)*, 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 in the research study.

8. 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. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance.

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

This study may not make your health better. However, Ibrutinib and Ixazomib combined together may provide better disease control than either drug individually.

10. 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 treatment with Ibrutinib which can be prescribed without participating in this study. Talk to the Principal Investigator or your doctor if you have any questions about any of these treatments or procedures.

11. 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:

- Study Drug (Ixazomib)
- Research lab tests
- Research Bone Marrow Tests
- Bone Marrow Biopsy at Cycle 2, Day 1

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:

- Standard of care drug (Ibrutinib)
- Standard of care lab testing

- Echocardiogram
- Physical Exams
- Research Bone Marrow Tests
- PET/CT imaging of your chest, abdomen, and pelvis
- Pregnancy tests, if applicable
- Bone Marrow Biopsy (except at Cycle 2, Day 1)

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

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

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

13. What will happen to your information and samples?

Your information or samples collected for this study will not be used or shared for future research studies even if the identifiable information such as your name, Mayo Clinic number or date of birth is removed.

Your samples will be used for this study. When the study is done, they will be destroyed.

14. 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 data and confidentiality of subjects data, a code will be used as an identifier. The code will be a registration number assigned specifically to the patient by Mayo Clinic, if applicable. The correlating Mayo Clinic number and the patient's 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.
- Researchers involved in this study at other institutions.
- The sponsor(s) of this study and the people or groups hired by the sponsor(s) to help perform this research.
- Takeda Pharmaceuticals, Inc.
- 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, unless otherwise specified in this consent form, 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, or 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 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.

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.

There is no expiration or end date related to the Sponsor's use of your health information received from Mayo Clinic as part of this study.

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