MC1382 / 13-000414

Phase 1/2 Trial of MLN9708 in Combination With Cyclophosphamide and Dexamethasone in Patients With Previously Untreated Symptomatic Multiple Myeloma

NCT01864018

Document Date: 01/06/2022

MAYO CLINIC

Name and Clinic Number

Approval Date: **January 6, 2022**
Not to be used after: **February 24, 2022**

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC1382: Cohort B-Phase 1/2 Trial of (MLN9708) ixazomib in Combination with Cyclophosphamide and Dexamethasone in Patients with Previously Untreated Symptomatic Multiple Myeloma or Light Chain Amyloidosis (Amyloidosis patients)

IRB#: 13-000414

Principal Investigator: Dr. S. Kumar 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.

MAYO CLINIC

Name and Clinic Number

Approval Date: **January 6, 2022**
Not to be used after: **February 24, 2022**

CONTACT INFORMATION

You can contact …	At …	If you have questions about …
Principal Investigators: Dr. Shaji Kumar Dr. Leif Bergsagel	**Phone:** (507) 284-2511 **Institution Name and Address:** Mayo Clinic 200 First Street SW Rochester, MN 55905 **Phone:** (480) 301-8000 **Institution Name and Address:** Mayo Clinic in Arizona 13400 East Shea Boulevard Scottsdale, AZ 85259	▪ 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

Approval Date: **January 6, 2022**
Not to be used after: **February 24, 2022**

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.

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

You are being asked to take part in this study because you have been diagnosed with a condition called Light Chain Amyloidosis that requires treatment.

The plan is to have about 87 people take part in this study at Mayo Clinic.

2. Why is this research study being done?

Various treatment options are available for treatment of your condition. One of the commonly used treatments is the combination of a drug called bortezomib with two other drugs, cyclophosphamide and dexamethasone. Ixazomib is similar to bortezomib (VELCADE), but can be given as a pill instead of injection. It is thought that Ixazomib will interfere with the process of protein breakdown in the plasma cells that are responsible for the light chain amyloidosis. This study is being done to find out the effects (good and bad) of treating amyloidosis with the combination of Ibixazomib, cyclophosphamide and dexamethasone.

The drug (Ixazomib) as used in this study is considered investigational, which means it has either not been approved by the Food and Drug Administration (FDA) for routine clinical use or for the use described in this study, however the FDA has approved the use in this research study.

Cyclophosphamide and dexamethasone are both FDA approved, however their use in this research study is considered investigational.

3. Information you should know

Who is Funding the Study?
Takeda Pharmaceuticals is funding the study. Takeda will pay the Principal Investigator or the institution to cover costs related to running the study.

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

You will be in the study for approximately three years.

5. 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:

Screening

- Complete medical history, physical exam, including, weight, vitals and height and assessment of your ability to carry out daily activities.
- Routine Blood and urine tests
- Skeletal survey
- Bone marrow aspirate and biopsy
- Chest x-ray
- Echocardiogram
- Neurological examination and nerve studies if there is nerve involvement
- Scan of the abdomen if there is suspicion of liver enlargement
- Pregnancy test
- A questionnaire to assess if you have any symptoms suggesting damage to the nerves

Every Cycle, Pretreatment

- Physical Exam, including, weight, vitals and height and assessment of your ability to carry out daily activities
- Routine Blood and urine tests
- A questionnaire to assess if you have any symptoms suggesting damage to the nerves (every cycle for the first 4 cycles, and then every 3 cycles)

- Patient medication diary
- X-ray skeletal survey (every 6 cycles)

Every 14 days (for 3 months)

- Routine Blood and urine tests

During The Study

- Bone marrow aspirate and biopsy will be done at the end of 4 cycles and 12 cycles of treatment, and an additional sample if required to confirm that your disease is in remission

Maintenance Phase:

- Physical Exam, including, weight, vitals and height and assessment of your ability to carry out daily activities
- Routine Blood and urine tests
- Patient medication diary (monthly)

As of amendment 12;
You may receive treatment locally, provided the ixazomib can be sent, and provided it is feasible to have the evaluations required by the protocol completed remotely or through your local healthcare facilities. You will need to return to the enrolling institution every 3rd cycle.

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

POTENTIAL DISCOMFORTS AND RISKS OF MLN9708

Based on studies of ixazomib it is possible to predict some of the discomforts and risks. However, it is possible that ixazomib may cause risks that have not yet been observed in patients. The following risks might be seen:

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

- Feeling sick to your stomach (Nausea)
- Throwing up (Vomiting)
- Loose Stool (Diarrhea)
- Constipation
- Feeling tired or weak

- 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 including shingles
- Decrease in red blood cells, which are the oxygen carrying cells which could make you feel tired (Anemia)
- Skin rash
- Swelling of extremities (arms and/or legs)
- Numbness and tingling (also known as peripheral neuropathy)
- Joint pain (arthralgia)
- Flu like symptoms and other upper respiratory tract infections
- Lung infections including pneumonia
- A painful blistery red rash that is confined to one side of the body, similar to chicken pox (Herpes zoster)

Less likely risks of Ixazomib (MLN9708) *(events occurring less than or equal to 20% of the time)*

- Decreased appetite
- Abdominal pain or distension
- Back pain
- Sensation of lightheadedness or vertigo (spinning sensation) (Dizziness)
- Blood chemical imbalance (Electrolyte imbalance)
- Excessive or abnormal loss of body fluids (Dehydration)

Rare risks of Ixazomib (MLN9708) *(events occurring less than 2-3% of the time)*

- Low or high blood pressure
- 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 (MLN9708)

- Life threatening severe skin rash
- Abnormal heart rhythms
- Worsening of your heart function (Congestive heart failure)
- Disorders 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 (Thrombotic Thrombocytopenic Purpura (TTP))
- 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. High creatinine 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).
- Blockage of your bowel function
- Severe rash that can lead to skin peeling and life threatening complications (Stevens Johnson syndrome)
- 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
- Acute febrile neutrophilic dermatosis (Sweet's syndrome), this is a skin condition that causes fever and a painful skin rash that appears mostly on the arms, face and neck.

Ixazomib (MLN9708) should not be taken if you have ever had a serious allergic reaction to boron or boron containing products.

Dexamethasone

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

- Stomach and throat ulcers or worsening of any ulcers you had before treatment
- Swelling and pain of the pancreas
- Weight gain around the stomach
- Puffiness (especially in the face)
- Buildup of fluids and a rise in blood pressure
- Possible rise in your blood sugar
- Changes in the blood levels of potassium
- Infection

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

- Muscle weakness
- Brittle bones
- Menstrual changes
- Itching, and other allergic reactions, some severe

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

- Mood swings
- Depression
- Trouble sleeping
- Changes in personality
- Seizures
- Dizziness
- Patients who are more likely to get heart disease may have heart failure

As with any medication, allergic reactions are a possibility.

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

Pregnancy and Birth Control:

RISK TO THE UNBORN CHILD (MEN AND WOMEN)
Female subjects: We do not know if the study drug Ixazomib will affect mother's milk or an unborn child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/ infant, you should not become pregnant or nurse a baby while on this study.

You must have a negative pregnancy test prior to enrolling in the study.

Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use two effective methods of birth control from the time of signing the informed consent form, for the entire study drug treatment period, and for 90 days after completing study drug treatment. It is strongly recommended that at least one of these two methods be highly effective (see examples below).

Highly effective methods	**Other effective methods (barrier methods)**
Intra-uterine devices (IUD)	Latex condom with a spermicidal agent
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; Cervical cap with a spermicide; Sponge with a spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

You must use birth control methods as directed above, unless you completely avoid having heterosexual intercourse.

Male subjects: We do not know if using Ixazomib will affect sperm. Therefore, due to potential risk, you should not get your partner pregnant during the study drug treatment period. Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex condom with a spermicidal agent) during the entire study drug treatment period, and for four months after completing study drug treatment. Or, you should completely avoid having heterosexual intercourse.

Highly effective methods	**Other effective methods (barrier**
Vasectomy	Latex condom with a spermicidal agent
	Diaphragm with spermicide; Cervical cap with spermicide; Sponge with spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

All subjects (male or female): If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female subjects who become pregnant while on this study, the study drug will be stopped immediately and the pregnancy will be followed until conclusion.

Risk summary

Many side effects go away shortly after the Ixazomib is stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death.

Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

Cyclophosphamide

Likely (happening greater than 20% of the time)

- Feeling sick to the stomach
- Throwing up
- Loss of appetite
- Watery stools
- Yellowing of the skin
- Lowering of your blood cell counts which could cause infection or bleeding and you may have to have a blood transfusion. Contact your study doctor right away if you develop any signs of infection such as fever, chills, persistent sore throat

Less likely (happening less than or equal to 20% of the time)

- Escape of the drug from the vein may cause soreness or severe pain and redness in that area; pain, redness, and soreness of a vein
- Temporary hair loss. Regrowth may have a different color or texture.

- Bladder irritation. This can cause pain, blood in the urine, unusual decrease in the amount of urine, dark urine, and scarring of the bladder. If you drink 8 to 10 glasses of water a day and empty the bladder frequently, you can avoid this side effect.
- Damage to the female sex organs. Women who are still having periods may not have them every month or they may stop altogether for a time. A woman may not be able to get pregnant again.
- Sores in the mouth

Rare but serious (happening less than 3% of the time)

- Secondary leukemia and/or myelodysplastic syndrome (damage to the bone marrow that affects normal blood cell production)
- Allergic reaction (rapid heartbeat, shortness of breath, wheezing, tightness in the throat)
- Black/bloody stools
- Severe stomach/abdominal pain
- Mental/mood changes
- Muscle weakness/spasms
- Swelling of the ankles/feet
- Sudden or unusual weight gain
- Headache
- Dizziness
- Metallic taste
- Abnormal liver tests
- Heart failure has been reported but rarely at the doses given in this study. This can also happen if cyclophosphamide is used in combination with radiation treatment or certain other chemotherapy drugs (e.g., doxorubicin). Seek immediate medical attention if you develop chest pain, jaw/left arm pain, trouble breathing, and irregular heartbeat.
- Scarring of the lungs causing coughing spells and shortness of breath

Side effects may be higher by using other drugs with cyclophosphamide. Phenobarbital raises the effect of cyclophosphamide on your blood cells. Other drug interactions have been reported. If you need anesthesia within 10 days of taking cyclophosphamide, you should let your anesthesiologist know about your treatment.

7. Are there reasons you might leave this research study early?

Taking part in this research study is your decision. You may decide to stop at any time. You should tell the researcher 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 researchers, the company supplying drug and funding, or Mayo may stop you from taking part in this study at any time:

- If it is in your best interest,
- If you do not follow the study rules,
- If the study is stopped.

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. If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other people with multiple amyloidosis in the future.

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

You do not have to be in this study to receive treatment for your condition. Your other choices may include other chemotherapy. You should talk to the researcher and your regular physician about each of your choices before you decide if you will take part in this study.

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 (MLN9708)

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 exam, including weight, vital signs, height
- ECOG performance status (Your ability to carry out daily activities, called your "performance status", will be evaluated)
- Routine Blood tests
- Chest x-ray
- Echocardiogram
- CT scans if indicated
- Neurological examination if indicated
- Bone marrow aspirate and biopsy
- Pregnancy test (for woman of child bearing potential)
- Standard of care drugs Cyclophosphamide and Dexamethasone

You will also be responsible for any co-payments and deductibles. Before you take part in this study, you should call your insurer to find out if the cost of these tests and/or procedures will be covered. You will have to pay for any costs not covered by your insurance.

If you have questions about any costs to you that may result from taking part in the research, please speak with the Principal Investigator. If you wish, arrangements can be made for you to speak with someone in Patient Account Services about these costs by calling 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 samples?

We would like to keep your sample for future research. You can still take part in this current study even if you don't want your sample used for future research. If you agree to give your sample, it will be the property of Mayo Clinic.

Other researchers at Mayo Clinic who aren't involved with this study may ask to use your sample for future research. Researchers at other institutions may also ask for a part of your sample for future studies. Your sample will be sent to researchers in a coded format, which protects your identity.

Some future studies may examine your DNA, which is the genetic information you inherited from your parents (genetic testing). The Principal Investigator may contact you if there are findings which may be useful for your health care. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

Please read the following statements and mark your choices:

1. I permit my sample to be stored and used in future research of Multiple Myeloma at Mayo Clinic:

☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my sample to be stored and used in future research at Mayo Clinic to learn about, prevent, or treat any other health problems:

☐ Yes ☐ No Please initial here: _____Date: _____

3. I permit Mayo Clinic to give my sample to researchers at other institutions:

☐ Yes ☐ No Please initial here: _____Date: _____

There is a very small chance that some commercial value may result from the use of your donated sample. If that happens, you won't be offered a share in any profits.

You may request to have your sample destroyed by writing to the Principal Investigator. The address is found in the "Contact Information" section of this consent form.

Because we cannot predict how your sample will be used in the future, we cannot promise that samples can be retrieved and 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. Various methods are used to safeguard confidentiality. Some or all of the following may be used in this study: assigning a specific code or registration number to each participant's data and samples, research materials stored in locked areas, password protected data stored on a computer. If the results of the research are made public, information that identifies you will not be used.

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.

Health information may be collected about you from:

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

Why will this information be used and/or given to others?

- To do the research.
- To report the results.
- To see if the research was done correctly.

If the results of this study are made public, information that identifies you will not be used.

Who may use or share your health information?

- Mayo Clinic research staff involved in this study.
- Takeda

With whom may your health information be shared?

- The Mayo Clinic Institutional Review Board that oversees the research.
- Other Mayo Clinic physicians involved in your clinical care.
- Researchers involved in this study at other institutions.
- 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.
- The sponsor(s) of this study and the people or groups it hires to help perform this research.
- A group that oversees the data (study information) and safety of this research.

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 Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission 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.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with Mayo Clinic.

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
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 lasts forever, unless you cancel it.

ENROLLMENT AND PERMISSION SIGNATURES

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

	/ /	: AM/PM
Printed Name	Date	Time

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.

	/ /	: AM/PM
Printed Name	Date	Time

Signature