A Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant

**Purpose**

The purpose of this study is to determine the effect of ixazomib citrate maintenance therapy on progression-free survival (PFS), compared to placebo, in patients with newly diagnosed multiple myeloma (NDMM) who have had a response (complete response [CR], very good partial response [VGPR], or partial response [PR]) to induction therapy followed by high-dose therapy (HDT) and autologous stem cell transplant (ASCT).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Myeloma</td>
<td>Drug: Ixazomib Citrate</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Autologous Stem Cell Transplant</td>
<td>Drug: Placebo</td>
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</tbody>
</table>

Study Type: Interventional  
Study Design: Allocation: Randomized  
Endpoint Classification: Efficacy Study  
Intervention Model: Parallel Assignment  
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)  
Primary Purpose: Treatment

Official Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Patients With Multiple Myeloma Following Autologous Stem Cell Transplant

Resource links provided by NLM:

**MedlinePlus** related topics:  
Multiple Myeloma

**Drug Information** available for:  
Sodium citrate  
Citric acid monohydrate

**Genetic and Rare Diseases Information Center** resources:  
Multiple Myeloma

**U.S. FDA Resources**

**Further study details as provided by Millennium Pharmaceuticals, Inc.:**

Primary Outcome Measures:

- Progression Free Survival (PFS) [ Time Frame: Every 28 days up to 24 months ] [ Designated as safety issue: No ]
PFS is defined as the time from the date of randomization to the date of first documentation of disease progression, as evaluated by an independent review committee according to International Myeloma Working Group (IMWG) criteria, or death due to any cause, whichever occurs first.

Secondary Outcome Measures:
- Overall Survival (OS) [Time Frame: Every 28 days from the Randomization date up to 110 months] [Designated as safety issue: No]
  OS will be measured as the time from the date of randomization to the date of death.
- Percentage of Participants who Achieve or Maintain Any Best Response Category during the Treatment Period [Time Frame: Up to 24 months] [Designated as safety issue: No]
  Response was assessed according to IMWG criteria. Best response includes partial response (PR), very good partial response (VGPR) and complete response (CR)
- Time to Progression (TTP) [Time Frame: From the date of randomization to the date of first documented progressive disease (up to 110 months)] [Designated as safety issue: No]
  TTP is defined as the time from the date of randomization to the date of first documentation of progressive disease, using IMWG criteria.
- Second Progression-Free Survival (PFS2) [Time Frame: Every 28 days from the randomization to 2nd disease progression or death (up to 110 months)] [Designated as safety issue: No]
  PFS2 is defined as the time from the date of randomization to the date of second documentation of progressive disease (PD), using IMWG criteria, or death due to any cause, whichever occurs first. The second PD should occur during or after the second line of antineoplastic therapy following study treatment but before the third line of therapy.
- Time to End of the Next Line of Therapy after Study Treatment [Time Frame: From the randomization to the date of last dose of the next line of therapy (up to 110 months)] [Designated as safety issue: No]
  Time to end of the next line of therapy is defined as the time from the date of randomization to the date of last dose of the next line of antineoplastic therapy following study treatment or death due to any cause, whichever occurs first.
- Duration of the Next Line of Therapy after Study Treatment [Time Frame: From the start of next line therapy to end of study (up to 110 months)] [Designated as safety issue: No]
  Duration of the next line of therapy is defined as the time from the date of the first dose of the next line of therapy to the date of the last dose of the next antineoplastic therapy following study treatment or death due to any cause, whichever occurs first.
- Percentage of Participants Who Develop A New Primary Malignancy [Time Frame: From the randomization date till death or termination of the study (up to 110 months)] [Designated as safety issue: No]
- Percentage of Participants with Conversion from Minimal Residual Disease (MRD) Positive to MRD Negative, or the Maintenance of MRD Negativity [Time Frame: Screening, Cycle 12 (± 2 cycles), and Cycle 24 (± 2 cycles)] [Designated as safety issue: No]
  Bone marrow aspirates and blood samples will be sent to a central laboratory and will be assessed for MRD using flow cytometry and a sequencing methodology. MRD negativity is defined as absence of MRD and MRD positivity is defined as presence of MRD.
- Correlation between Minimal Residual Disease (MRD) Status and Progression Free Survival (PFS) and Overall Survival (OS) [Time Frame: Up to 110 months] [Designated as safety issue: No]
  Correlation will be determined using bone marrow aspirates and blood samples.
- Association between Mutations in Key Signaling Pathways in Multiple Myeloma and response, PFS and OS [Time Frame: Every 28 days up to 110 months] [Designated as safety issue: No]
  Key signaling pathways will include RAS/RAF (a pathway necessary for normal cell function) response, progression free survival (PFS), and overall survival (OS) and will be evaluated using archival materials and tumor DNA from bone marrow aspirates.
- Relationship between Polymorphisms in Proteasome and Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NFkB)-Related Genes or circulating proteasome levels, and response, PFS, and OS [Time Frame: Screening] [Designated as safety issue: No]
  NFkB-related genes will include genes such as proteasome (prosome, macropain) subunit, beta type, 1 (PSMB1) and tumor necrosis factor receptor-associated factor 3 (TRAF-3), or circulating proteasome levels, and response, time-to-progression (TTP), progression-free survival (PFS), and overall survival (OS), and will be evaluated using blood samples.
- Overall (OS) Survival in a High-Risk Population [Time Frame: From randomization up to 110 months] [Designated as safety issue: No]
High-risk population will include but not be limited to participants carrying deletion (del)17, t(4:14), t(14:16), amplification (ampl) 1q, del13, or del1p. OS will be measured as the time from the date of randomization to the date of death.

- Percentage of Participants with Adverse Events (AEs) [Time Frame: First dose of study drug through 30 days after last dose of study drug every 28 days up to 24 months] [Designated as safety issue: Yes]
  Adverse events are defined as any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal product reported from first dose of study drug through 30 days after the last dose of study drug.

- Change from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) QLQ-C30 [Time Frame: Baseline and every 28 days up to 24 months] [Designated as safety issue: No]
  The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) QLQ-C30 is completed by the patient. The EORTC QLQ-30 contains 30 questions that incorporate 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The patient answers questions about their health during the past week. There are 28 questions answered on a 4-point scale where 1=Very poor (worst) to 4=Very Much (worst) and 2 questions answered on a 7-point scale where 1=Very poor (worst) to 7=Excellent (best).

- EuroQol 5-Dimensional Health Questionnaire (EQ-5D) [Time Frame: Every 28 days during treatment and PFS follow-up and every 12 weeks during OS follow-up (up to 110 months)] [Designated as safety issue: No]
  The EQ-5D consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises 5 dimensions (mobility, self care, usual activities, pain/discomfort, and anxiety/depression). The patient answers 5 questions about their health on that day and checks one of 3 boxes: no problems/pain/anxiety or depression, moderate problems/pain/anxiety or depression, or extreme problems/pain/anxiety or depression. The EQ VAS records the respondent's self-rated health on a 100 mm vertical visual analogue scale ranging from 0 bottom of the scale (worst imaginable health state) to 100 top of the scale (best imaginable health state).

- Pharmacokinetic Parameter: Plasma Concentration of Ixazomib [Time Frame: Cycle 1, Day 1 postdose at 1 and 4 hours and Cycle 1 predose on Days 8 and 15; Cycle 2 predose on Days 1 and 8; Cycles 3- through 10 on Day 1 predose] [Designated as safety issue: No]
  Plasma concentrations of the complete hydrolysis product of ixazomib citrate (ixazomib) will be measured using a validated Liquid Chromatography-tandem Mass Spectrometry (LC/MS/MS) assay.

- Time to Resolution of Peripheral Neuropathy (PN) Events [Time Frame: From randomization date through 30 days after the last dose of drug (up to 24 Months)] [Designated as safety issue: No]
  Peripheral neuropathy (PN) is defined as the treatment-emergent adverse event in the high-level term of peripheral neuropathies not elsewhere classified (NEC) according to the Medical Dictionary for Regulatory Activities (MedDRA). A PN event is considered as resolved if its final outcome is resolved with no subsequent PN event of the same preferred term occurring on the resolution date or the day before and after. Time to resolution is defined as the time from the initial onset date (inclusive) to the resolution date for resolved events.

- Time to Improvement of Peripheral Neuropathy (PN) Events [Time Frame: From randomization date through 30 days after the last dose of drug (up to 25 months)] [Designated as safety issue: No]
  Peripheral neuropathy is defined as the treatment-emergent adverse event in the high-level term of peripheral neuropathies not elsewhere classified (NEC) according to Medical Dictionary for Regulatory Activities (MedDRA). A PN event is considered as improved if the event improves from the maximum grade. That is, all the grades recorded after the maximum grade is less than the maximum grade. Time to improvement is defined as the time from the initial onset date (inclusive) of the maximum grade to the first onset date that the toxicity grade is below the maximum grade with no higher grade thereafter, or the resolution date, whichever occurs first.

- Progression Free Survival (PFS) in a High-Risk Population [Time Frame: At the time of screening; day 1 of each cycle; at EOT and thereafter every 4 weeks until disease progression (up to 110 months)] [Designated as safety issue: No]
  High-risk population will include but not be limited to participants carrying deletion (del)17, t(4:14), t(14:16), amplification (ampl) 1q, del13, or del1p. PFS is defined as the time from the date of randomization to the date of first documentation of disease progression.

- Percentage of Participants with Serious Adverse Events (SAEs) [Time Frame: Will be collected from signing of the informed consent form through 30 days after the last dose of study drug] [Designated as safety issue: Yes]

- Assessment of Clinical Laboratory Values [Time Frame: From First dose date of study drug through 30 days after the last dose of study drug (up to 25 months)] [Designated as safety issue: Yes]

- Eastern Cooperative Oncology Group (ECOG) Performance Score [Time Frame: Up to 24 months] [Designated as safety issue: No]
  The ECOG performance is a 6-point scale used by doctors to assess how a patient's disease is progressing, how the disease affects the patient's daily life, and to determine appropriate treatment and prognosis. The scale is 0=Normal activity. Fully active, able to carry on all predisease performance without restriction (best) to 5=Dead.
Change from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EOTRC) multiple myeloma module QLQ MY-20 [Time Frame: Baseline and every 28 days during treatment and PFS follow-up and every 12 weeks during OS follow-up (up to 110 months)] [Designated as safety issue: No]

The EOTRC multiple myeloma module QLQ MY-20 is a patient-completed, 20-question quality of life questionnaire that has 4 independent subscales, 2 functional subscales (body image, future perspective), and 2 symptoms scales (disease symptoms and side-effects of treatment). The patient answers questions about their health during the past week using a 4-point scale where 1=Not at All to 4=Very Much.

Estimated Enrollment: 652
Study Start Date: July 2014
Estimated Study Completion Date: July 2023
Estimated Primary Completion Date: February 2018 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
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<tbody>
<tr>
<td>Experimental: ixazomib Citrate</td>
<td>Drug: ixazomib Citrate</td>
</tr>
<tr>
<td>ixazomib citrate 3 mg, capsule, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. ixazomib citrate 3 or 4 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26. Participants experiencing adverse events (AEs) attributed to study drug during any cycle may continue in the study but may have doses of study drug held or reduced by at least 1 dose level. Reduced doses are: 3 mg, 2.3 mg, 1.5 mg and discontinuation of study drug.</td>
<td>ixazomib citrate capsules</td>
</tr>
<tr>
<td>Placebo Comparator: Placebo</td>
<td>Drug: Placebo</td>
</tr>
<tr>
<td>ixazomib citrate placebo-matching 3 mg capsule, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. ixazomib citrate placebo-matching 3 or 4 mg capsules, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26. Participants experiencing adverse events (AEs) attributed to study drug during any cycle may continue in the study, but may have doses of study drug held or reduced by at least 1 dose level. Reduced doses are: 3 mg, 2.3 mg, 1.5 mg and discontinuation of study drug.</td>
<td>ixazomib citrate placebo-matching capsules</td>
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**Detailed Description:**
The investigational drug being tested in this study is called ixazomib citrate. Ixazomib citrate is being tested to slow disease progression and improve overall survival in people who have newly diagnosed multiple myeloma (NDMM) who have had any type of positive response to induction therapy followed by high-dose therapy (HDT) and autologous stem cell transplant (ASCT). This study will look at the effect of ixazomib citrate has on the length of time that participants are free of disease progression and their overall survival.

The study will enroll approximately 652 patients. Participants will be randomly assigned (by chance, like flipping a coin) to one of the two treatment groups—which will remain undisclosed to the patient and study doctor during the study (unless there is an urgent medical need):

- **Ixazomib citrate 3 mg**
- **Placebo (dummy inactive pill) - this is a capsule that looks like the study drug but has no active ingredient**

All participants will be asked to take one capsule on Days 1, 8 and 15 of each 28-day cycle, for up to 26 cycles.

This multi-center trial will be conducted globally. The overall time to participate in this study is up to 24 months. Participants will make 28 visits to the clinic during the treatment period and will continue to make follow-up visits every 4 weeks until the next line of therapy begins. Participants will also be contacted by telephone every 12 weeks after last treatment visit for a follow-up assessment.

**Eligibility**

**Ages Eligible for Study:** 18 Years and older

**Genders Eligible for Study:** Both

**Accepts Healthy Volunteers:** No

**Criteria**

**Inclusion Criteria:**

1. Adult male or female participants 18 years or older with a confirmed diagnosis of symptomatic multiple myeloma according to standard criteria.

2. Documented results of cytogenetics/fluorescence in situ hybridization (FISH) obtained at any time before transplant, and International Staging System (ISS) staging at the time of diagnosis available.

3. Underwent standard of care induction therapy (induction therapy must include proteasome inhibitor (PI) and/or immunomodulating drugs (IMiD)-based regimens as primary therapy for multiple myeloma), followed by a single autologous stem cell transplant (ASCT) with a high-dose melphalan (200 mg/m^2) conditioning regimen, within 12 months of diagnosis. Vincristine, Adriamycin [doxorubicin], and
Dexamethasone (VAD) is not an acceptable induction therapy for this trial.

4. Started screening no earlier than 75 days after transplant, completed screening within 15 days, and randomized no later than 115 days after transplant.

5. Must have not received post-ASCT consolidation therapy.

6. Documented response to ASCT (partial response [PR], very good partial response [VGPR], complete response [CR]/stringent complete response [sCR]) according to International Myeloma Working Group (IMWG) criteria.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

8. Female participants who:
   - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, AND
   - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the participant. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

9. Male participants, even if surgically sterilized (ie, status post vasectomy), who:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, AND
   - Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the participant. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the participant at any time without prejudice to future medical care.

10. Suitable venous access for the study-required blood sampling.

11. Is willing and able to adhere to the study visit schedule and other protocol requirements.

12. Must meet the following clinical laboratory criteria at study entry:
   - Absolute neutrophil count (ANC) ≥ 1,000/mm^3 and platelet count ≥ 75,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before randomization.
   - Total bilirubin ≤ 1.5 * the upper limit of the normal range (ULN).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 * ULN.
   - Calculated creatinine clearance ≥ 30 mL/min.

Exclusion Criteria:

1. Multiple myeloma which has relapsed following primary therapy or is not responsive to primary therapy. For this study, stable disease following ASCT will be considered nonresponsive to primary therapy.

2. Double (tandem) ASCT.

3. Radiotherapy within 14 days before the first dose of study drug.

4. Diagnosed or treated for another malignancy within 5 years before randomization or previously diagnosed with another malignancy with evidence of residual disease. Participants with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

5. Female participants who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.

6. Major surgery within 14 days before randomization.

7. Central nervous system involvement.

8. Infection requiring intravenous (IV) antibiotic therapy or other serious infection within 14 days before randomization.

9. Diagnosis of Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.

10. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

11. Systemic treatment with strong inhibitors of cytochrome P450s (CYP)1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapenten, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before randomization in the study.

12. Active hepatitis B or C virus infection, or know human immunodeficiency virus (HIV) positive.

13. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the participant inappropriate for entry into this study or interfere significantly with the assessment of safety and toxicity of the prescribed regimen (eg, peripheral neuropathy that is Grade 1 with pain or Grade 2 or higher of any cause).
14. Psychiatric illness/social situation that would limit compliance with study requirements.
15. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
16. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or gastrointestinal (GI) procedure that could interfere with the oral absorption or tolerance of treatment.
17. Treatment with any investigational products within 60 days before the first dose of the study drug regimen.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02181413

Contacts

Contact: Takeda Study Registration Call Center +1-877-825-3327 medicalinformation@tpna.com

Sponsors and Collaborators

Millennium Pharmaceuticals, Inc.

Investigators

Study Director: Medical Director Clinical Science Millennium Pharmaceuticals, Inc.

More Information

No publications provided

Responsible Party: Millennium Pharmaceuticals, Inc.

ClinicalTrials.gov Identifier: NCT02181413 History of Changes

Other Study ID Numbers: C16019, U1111-1155-8695, 2013-002076-41, C16019CTIL

Study First Received: June 27, 2014

Last Updated: December 3, 2014

Health Authority:
- United States: Food and Drug Administration
- Austria: Federal Office for Safety in Health Care
- Belgium: Federal Agency for Medicinal Products and Health Products
- Canada: Health Canada
- Czech Republic: State Institute for Drug Control
- Denmark: Danish Medicines Agency
- France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis)
- Germany: Federal Institute for Drugs and Medical Devices
- Italy: The Italian Medicines Agency
- Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)
- Norway: Norwegian Medicines Agency
- Portugal: National Pharmacy and Medicines Institute
- Singapore: Health Sciences Authority
- Sweden: Medical Products Agency
- United Kingdom: Medicines and Healthcare Products Regulatory Agency

Keywords provided by Millennium Pharmaceuticals, Inc.:

Drug therapy
- TOURMALINE
- ixazomib

Additional relevant MeSH terms:
- Multiple Myeloma
- Neoplasms, Plasma Cell
- Blood Protein Disorders
- Cardiovascular Diseases
- Hematologic Diseases
- Hemorrhagic Disorders
- Vascular Diseases
- Citric Acid
- Glycine
- Anticoagulants
- Chelating Agents
- Glycine Agents