A Phase 3 Randomized, Controlled, Open-label, Multicenter, Safety and Efficacy Study of Dexamethasone Plus MLN9708 or Physician's Choice of Treatment Administered to Patients With Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis

Published: 21-08-2012
Last updated: 26-04-2024

As of protocol Amendment 06, evaluation of the safety profile of MLN9708 and/or other study medication is the only endpoint being assessed. All other study endpoints will no longer be assessed.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON50586

Source
ToetsingOnline

Brief title
MLN9708 (C16011; 0114/0065)

Condition

- Plasma cell neoplasms

Synonym
primary amyloidosis, primary systemic amyloidosis (PSA)

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: by the sponsor;Millennium Pharmaceuticals

Intervention

Keyword: MLN9708, Phase 3, Systemic Light Chain Amyloidosis

Outcome measures

Primary outcome

As of protocol Amendment 06, evaluation of the safety profile of MLN9708 and/or other study medication is the only endpoint being assessed. All other study endpoints will no longer be assessed.

Secondary outcome

As of protocol Amendment 06, evaluation of the safety profile of MLN9708 and/or other study medication is the only endpoint being assessed. All other study endpoints will no longer be assessed.

Study description

Background summary

As of protocol amendment 06, evaluation of the safety profile of MLN9708 and/or other study medication is the only endpoint being assessed. All other study endpoints will no longer be assessed. Please find the original study background here:

Primary light chain (AL) amyloidosis is a rare, lethal plasma cell dyscrasia in which fibril deposits containing toxic monoclonal immunoglobulin light chains infiltrate tissues causing their dysfunction and failure. Unlike patients with MM, patients with AL amyloidosis not only have a hematologic malignancy, but also direct progressive involvement of 1 or more visceral organs. Given the

rarity of AL amyloidosis, there have not been any randomized controlled trials in the relapsed disease setting, but rather there have been anecdotal case reports, retrospective series, and small single institution trials utilizing differing single-agent or combination therapy regimens shown active in a similar yet different plasma cell dyscrasia multiple myeloma. The National Comprehensive Cancer Network (NCCN) therefore recommends treatment in a clinical trial because there are no regulatory approved treatments and data are insufficient to identify an optimal therapy.(4) The treatment of patients with relapsed and/or refractory systemic light-chain (AL) amyloidosis is an area of unmet need. The current therapeutic approach to systemic amyloidosis is based on the observation that amyloid deposits can be reabsorbed and organ function restored if the concentration of the amyloidogenic protein precursor (known as the involved free light chains [FLC]) is reduced. Therefore, the aim of therapy in AL amyloidosis is to rapidly decrease the supply of errant amyloid-forming FLC by suppressing the underlying clonal plasma cell while using supportive measures to sustain and possibly preserve organ functions. The clinical course of the disease is improved by arresting progressive organ damage and allowing functional improvement of affected organs, thereby providing clinical benefit.

While reduction in the amyloidogenic-involved free light chains can improve the clinical course of the disease, the therapies that achieve these results are not curative adding to the uniformly fatal prognosis for this disease with the currently available approaches. When the patient*s disease relapses or does not respond to first-line therapy, there is no standard therapy, and data are limited even for those agents used in this setting.(4) Unfortunately, the current choice of treatment is primarily based on nonrandomized studies and investigator personal experience, which accounts for discrepancies in the treatment strategies proposed by different investigators. Because there is no consensus, the choice of treatment depends on a fine balance between the perceived efficacy of the chosen regimen and the individual patient*s expected ability to tolerate the treatment*s toxicity considering their age, organ dysfunction, and pace of disease, and given the limited treatment options, may mean exposure to an agent from the same drug class. Available treatment options in AL amyloidosis have used advances made in the chemotherapy of MM, including the use of corticosteriods, alkylating agents, proteasome inhibitors, and immunomodulatory agents (IMiDs), more frequently as combination regimens but also as single agents.

Recognizing that proteasome inhibition is an effective anticancer therapeutic approach, Millennium developed MLN9708, which is a modified dipeptide boronic acid proteasome inhibitor similar to VELCADE, with the aim of improving the pharmacology of the agent, improving drug administration, while building on the efficacy seen with VELCADE. This study has been designed based on the results of VELCADE in previously treated AL amyloidosis,(80, 87) the emerging activity seen with MLN9708 in the treatment of previously treated and untreated MM and AL amyloidosis (see Section 1.3), and the urgent need for better treatment options for this rare disease, especially in the relapsed setting where no standard treatment exists.

Amyloidosis is a protein misfolding disease and may therefore be particularly sensitive to proteasome inhibition. The hypothesis of this study, therefore, is to compare a proteasome inhibitor, oral MLN9708, to oral agents of other drug classes that are currently used in clinical practice. Given that the AL amyloidosis population is predominantly a frail and elderly patient population, the convenience of an oral regimen is expected to increase compliance and possibly duration of treatment, which in turn should result in more durable hematologic responses. This study is designed to determine the safety and efficacy of oral MLN9708 with dexamethasone compared with treatment as chosen by the investigator from a selected list of oral regimens routinely available in clinical practice, dexamethasone alone or with an alkylating agent (melphalan or cyclophosphamide) or dexamethasone with an IMiD (thalidomide or lenalidomide) in patients with relapsed AL amyloidosis. Inclusion of patients with amyloid involvement of heart and kidney was selected because these organs represent the major organs most commonly involved in AL amyloidosis, but more importantly, the criteria for involvement, response, and progression are based on objective clinical laboratory and imaging tests which can be analyzed by central laboratories to reduce variability and bias. The primary objective of this study is to determine the overall hematologic response based on dFLC (difference between the involved and uninvolved FLC) assessment and to determine the rate of vital organ (that is heart and kidney) deterioration at 2 years. An improvement in hematologic response, as measured by reduction in FLC, and a reduction in the rate of vital organ deterioration in patients with relapsed or refractory systemic light chain amyloidosis would represent clinical benefit.

Study objective

As of protocol Amendment 06, evaluation of the safety profile of MLN9708 and/or other study medication is the only endpoint being assessed. All other study endpoints will no longer be assessed.

Study design

This is a phase 3, randomized, controlled, open-label, multicenter study of the oral formulation of dexamethasone plus MLN9708 compared with treatment chosen by the investigator from a prespecified list of regimens available in clinical practice. Treatment options will include: dexamethasone alone, dexamethasone plus an alkylating agent (melphalan or cyclophosphamide), or dexamethasone plus an immunomodulatory drug (IMiD, thalidomide or lenalidomide) in patients with relapsed or refractory AL amyloidosis. Crossover to the investigational treatment arm is not permitted during participation in this study.
Eligible patients must have: 1) biopsy-proven AL amyloidosis with relapsed or refractory disease despite 1 or 2 prior therapies; 2) disease requiring further treatment; 3) measureable disease as defined by serum differential free light chain concentration (dFLC); and 4) objective and measurable major organ

involvement (ie, cardiac or renal) as defined by the standard International Society of Amyloidosis (ISA) criteria. Patients must not have been previously treated with proteasome inhibitors. (The sponsor reserves the right to open the trial to proteasome inhibitor-exposed patients in the future, at some time point after the first interim analysis.)
Physicians will choose a treatment regimen from a list of options provided by the sponsor. Before randomization, physicians will declare which treatment regimen they plan to select for each screened patient; the selection will be recorded in the database. To maintain a balanced representation of the disease characteristics, patients enrolled in this study will be stratified by: 1) Cardiac Risk Stage: 1 versus 2 versus subgroup Cardiac Risk Stage 3 (ie, both NT-proBNP and troponin T over threshold [but NT-proBNP < 8000 pg/mL]); 2) relapsed versus refractory (relapsed is defined as PD documented more than 60 days after last dose; refractory is defined as documented absence of hematologic response or hematologic progression on or within 60 days after last dose of prior therapy); and 3) proteasome inhibitor naïve versus exposed.
Eligible patients will be randomized in a 1:1 ratio into 1 of the 2 study arms:
Arm A: dexamethasone plus MLN9708
Arm B: physician*s choice
In both treatment arms, each patient will continue to receive sequential cycles of therapy until disease progression, unacceptable toxicity, or until the study is terminated, whichever occurs first.
Response to therapy will be evaluated by an AC which will include the assessment of hematologic response and organ response according to the criteria outlined in the Revised Consensus Response Criteria of the ISA. The AC will also review specific data elements and corresponding data documentation to support criteria of vital organ (that is heart or kidney) deterioration. An independent data monitoring committee (IDMC) will review safety and efficacy data at the interim analyses.
Safety will be assessed through adverse events (AEs), clinical laboratory tests, and vital sign measurements. In addition, QOL and HU will be assessed using questionnaires.
After disease progression, patients will be followed for survival, vital organ deterioration, and subsequent therapy at least every 12 weeks
As of Amendment 6, however, the first IA has been conducted and the primary endpoint of overall hematologic response rate (CR + VGPR + PR) did not reach statistical significance. As such, the sponsor has decided to remove the planned second IA and final analysis and discontinue the majority of study assessments to ease the burden of protocol-mandated assessments on patients. Ixazomib (MLN9708) and control drugs (if Takeda has been supplying them) will continue to be provided for patients who continue to derive benefit.
Upon implementation of this amendment, data collection requirements will be limited to the following safety assessments: all SAEs (regardless of causality, including all deaths), any AE resulting in dose modification or discontinuation of any study drug, Grade >=3 AEs, AEs of new primary malignancy, all reports of drug exposure during pregnancy and pregnancy outcomes, product complaints, and medication errors (including overdose). All other study assessments are no

longer required. Central laboratory and investigator assessments of response and progression for protocol purposes are discontinued*AC review of response data and IDMC review of efficacy and safety data will no longer be performed. Patients will not be followed for the PFS or OS follow-up periods, as PFS and OS are no longer being collected. Quality of Life (QOL) and pharmacokinetic (PK) assessments will no longer be performed or recorded. Patients should otherwise be treated by the investigator according to standard of care.

Intervention

Eligible patients will be randomized in a 1:1 ratio into 1 of the 2 study arms:
Arm A: dexamethasone plus MLN9708
Arm B: physician*s choice

Study burden and risks

Please refer to the Investigator Brochure for the Safety Information.

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonization (ICH) guidelines. Please refer to section E9 for a detailled description of the risks and side effects.

Contacts

Public
Millenium Pharmaceuticals

Landsdowne Street 40
Cambridge, MA 02139
US
Scientific
Millenium Pharmaceuticals

Landsdowne Street 40
Cambridge, MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female patients 18 years or older., 2. Biopsy-proven diagnosis of AL amyloidosis according to the following standard criteria:, a. Histochemical diagnosis of amyloidosis, as based on tissue specimens with Congo red staining with exhibition of an apple-green birefringence, b. If clinical and laboratory parameters insufficient to establish AL amyloidosis or in cases of doubt, amyloid typing may be necessary (see Section 15.1), 3. Measurable disease as defined by serum differential free light chain concentration
(dFLC, difference between amyloid forming [involved] and nonamyloid forming [uninvolved] free light chain [FLC]) >= 50 mg/L)., 4. Objective, measurable major (cardiac or renal) organ amyloid involvement as defined as follows (amyloid involvement of at least 1 required):
a. Cardiac involvement is defined as the presence of a mean left ventricular wall thickness on echocardiogram greater than 12 mm in the absence of other potential causes of left ventricular hypertrophy (controlled hypertension is allowed) with a noncardiac biopsy showing amyloid, or a positive cardiac biopsy in the presence of clinical or laboratory evidence of involvement. If there is isolated cardiac involvement, then typing of amyloid deposists is recommended.
b. Renal involvement is defined as proteinuria (predominantly albumin) > 0.5 g/day in a 24- hour urine collection
Note: Amyloid involvement of other organ systems is allowed, but not required., 5. Must be relapsed or refractory after 1 or 2 prior therapies.
For this protocol, relapsed is defined as PD documented more than 60 days after last dose; refractory is defined as documented absence of hematologic response or hematologic progression on or within 60 days after last dose of prior therapy.
a. Patient must not have been previously treated with proteasome inhibitors. (The sponsor reserves the right to open the study to proteasome inhibitor-exposed patients in the future, at some time point after the first IA. In that case, the patient may not be refractory to proteasome inhibitor therapy.), b. Given that the physician may select from an offered list of regimens to treat a, specific patient, the patient may be refractory to an agent/s listed within the list of offered treatment choices,

c. Must have recovered (ie, <= Grade 1 toxicity or patient*s baseline status) from the reversible effects of prior therapy, d. If a patient has received a transplant as his/her first-line therapy, he/she must be, at least 3 months posttransplantation and recovered from the side effects of the, stem cell transplant6. Patient must meet criteria for 1 of the following AL Amyloidosis Risk Stages (as defined, by NT-proBNP cut off of < 332 pg/mL and troponin T cut-off of 0.035 ng/mL as, thresholds):, a. Stage 1: both NT-proBNP and troponin T under threshold, b. Stage 2: either NT-proBNP or troponin T [but not both] over threshold;, c. Stage 3: both NT-proBNP and troponin T over threshold (but NT-proBNP, < 8000 pg/mL), 7. ECOG Performance Status <= 2, 8. Clinical laboratory values:, a. Absolute neutrophil count >= 1000/µL, b. Platelet count >=75,000/µL
c. Total bilirubin <= 1.5 x ULN except for patients with Gilbert's syndrome as defined by > 80% unconjugated bilirubin and total bilirubin <= 6 mg/dL, d. Alkaline phosphatase <= 5 x ULN,, e. ALT or AST <=3 x ULN, f. Calculated creatinine clearance >= 30 mL/min, 9. Female patients who:, a. 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 treatment, AND, b. Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR, c. Agree to practice true abstinence when this is in line with the preferred and ususal lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.), Male patients, even if surgically sterilized (ie, status post vasectomy), who:, a. Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, AND, b. Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR, c. Agree to practice true abstinence when this is in line with the preferred and ususal lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.), 10. 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 patient at any time without prejudice to future medical care.

Exclusion criteria

Prospective patients will be excluded from this study if they meet ANY of the following criteria:, 1. Amyloidosis due to mutations of the transthyretin gene or presence of other, non-AL amyloidosis., 2. Female patients who are lactating, breastfeeding, or pregnant., 3. Medically documented cardiac syncope, uncompensated NYHA Class 3 or 4 congestive heart failure (Section 15.6), myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant repetitive ventricular arrhythmias despite

antiarrhythmic treatment, or severe orthostatic hypotension or clinically important autonomic disease., 4. Clinically overt multiple myeloma, according to the IMGW criteria with at least 1 of the following:
a. Bone lesions
b. Hypercalcemia, defined as a calcium of > 11 mg/dL, 5. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or GI procedure that could interfere with the oral, absorption or tolerance of treatment., 6. Requirement for other concomitant chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered to be investigational or which would be considered as a treatment of AL amyloidosis. However, patients may be on chronic steroids (maximum dose 20 mg/day prednisone or equivalent [Section 15.7]) if they are being given for, disorders other than amyloidosis (eg, adrenal insufficiency, rheumatoid arthritis, etc.)., 7. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens., 8. Ongoing or active infection, known HIV positive, active hepatitis B or C infection., 9. Psychiatric illness/social situations that would limit compliance with study requirements., 10. Known allergy to boron, MLN9708, any of the study treatments, their
analogues, or excipients.
11. Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before the first dose of study treatment., 12. Diagnosed or treated for another malignancy with 3 years (or 5 years in France) before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-01-2013
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alkeran
Generic name:	Melphalan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cyclophosphamide
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Dexamethasone
Generic name:	Dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MLN9708
Generic name:	Ixazomib
Product type:	Medicine
Brand name:	Thalidomide
Generic name:	Thalidomide
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-08-2012

Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-10-2012
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-12-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-01-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-02-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-03-2013
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-03-2014
Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	24-03-2014

Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	30-04-2014
Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	20-05-2014
Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	18-08-2014
Application type:	Amendment
Review commission:	METOPP: Medisch Ethische Toetsing Onderzoek bij Patienten en Proefpersonen (Tilburg)
Approved WMO Date:	09-09-2014
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-09-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-07-2016
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-07-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-11-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-11-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-02-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-01-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-09-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-08-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-005468-10-NL
ClinicalTrials.gov	NCT01659658
CCMO	NL41603.028.12

Study results

Results posted: 18-07-2023

Summary results
Trial ended prematurely

First publication
06-02-2023