A Phase II Study Of Oral LBH589 In Adult Patients With Multiple Myeloma Who Have Received At Least Two Prior Lines Of Therapy And Whose Disease Is Refractory To The Most Recent Line Of Therapy

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PrimaryTo determine the hematological response (complete response(CR) / partial response (PR)) rate as per Bladé criteria to treatment with oral LBH589 of patients with MM who have received at least two prior lines of therapy and whose disease is...

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

Summary

ID

NL-OMON30969

Source
ToetsingOnline

Brief title
LBH589 in treatment of refractory Multiple Myeloma

Condition

- Plasma cell neoplasms
- Plasma cell neoplasms

Synonym
Multiple Myeloma; Kahler□s disease

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Financiering door de sponsor (Novartis Pharma)

Intervention

Keyword: LBH589, Multiple Myeloma, oral

Outcome measures

Primary outcome

Hematologic response: measurements as per Bladé criteria, including levels of serum M-protein, serum FreeLite (TM), Bence-Jones protein in urine, bone marrow differential, skeletal survey (on indication) for osteolytic lesions as well as radiological examiniations in case of extramedullar plasmacytomas.

Secondary outcome

Determination and calculation of disease evaluation per criteria in Bladé (1998) and per Durie (2006) using the parameters as described in the primary parameters.

Safety and tolerability will be evaluated using assessments of (serious) adverse events (frequency) and laboratory data (new, worsening or improving values) using the CTCAE Grading scales.

Study description

Background summary

Multiple myeloma (MM) is an incurable plasma cell malignancy characterized by

the proliferation and accumulation of clonal plasma cells. MM accounts for about 10% of hematological malignancies. In the majority of cases, myeloma clonal plasma cells produce an abundance of a single monoclonal immunoglobulin protein. Rarely, in oligo-secretory or non-secretory myeloma, very little amounts or no light or heavy chains are detectable in serum or urine.

Treatment has improved lately. However this has not resulted in cure of the disease. Therefore there is a medical need to investigate new therapies.

The malignant proliferation of plasma cells results in skeletal destruction (due to lytic lesions or osteoporosis) along with other common clinical symptoms of anemia, renal insufficiency and hypercalcemia.

LBH589 belongs to the emerging *epigenetic therapies*, and is an orally-administered histone deacetylase inhibitor (HDACi). It acts on chromatin and transcription factors, and modulates gene regulation including tumor suppressor genes. Pre-clinical studies demonstrates that LBH589 induces apoptosis or differentiation in multiple MM cell lines including those resistant to conventional therapies.

Study objective

Primary
To determine the hematological response (complete response(CR) / partial response (PR)) rate as per Bladé criteria to treatment with oral LBH589 of patients with MM who have received at least two prior lines of therapy and whose disease is refractory to the most recent line of therapy.

Secondary:
1. disease evaluation as per criteria in Bladé (1998)
a. overall response (CR/PR/MR) rate
b. clinical benefit (CR/PR/MR/SD) rate
c. duration of response (CR/PR)
d. time to response (CR/PR)
e. the progression-free survival (PFS)
2. response as per disease evaluation criteria Durie (2006)
3. the safety and tolerability of oral LBH589
4. the pharmacokinetics (PK) of LBH589
5. the correlative science data including data for common chromosomal abnormalities of MM, Cyclin D1 protein expression, bone markers, and angiogenesis markers that might correlate with efficacy and response.

Study design

A phase II, single arm, open label, multi-centre, study of oral LBH589.

A three-stage design will be used to test the null hypothesis that the response rate is 10% or less against the alternative hypothesis that the response rate is greater than 10%

In stage 1: 36 patients will be enrolled. At least 4 responders are required to be observed to initiate enrollment into stage 2. Otherwise enrollment will be stopped and the null hypothesis will not be rejected.
In stage 2: In the second stage, 36 additional patients will be enrolled. At least 9 responders are required to be observed among the enrolled 72 patients, in order to initiate enrollment into stage 3. Otherwise, enrollment will be stopped and the null hypothesis will not be rejected.
In stage 3: In the third stage of enrollment, an additional 72 patients will be enrolled. At least 22 responders are required to be observed within all 144 patients to reject the null hypothesis.

Intervention

This is an open label study. All of the patients will be receiving the same treatment regimen. LBH589 will be administered orally, 20mg once-a-day on MWF, every week.

Study burden and risks

Possible side effects of LBH589.

There will be additional visits and assessments during the treatment phase. These additional assessments (including ECG monitoring) are for reasons of safety and monitoring efficacy.
Additional bloodsamples are needed for pharmacokinetic evaluation and monitoring of thyroid function. Additional MUGA scans, cardiografie and ECGs are taken for reason of cardiac safety. Possibly for efficacy additional bone marrow biopsies or radiological imaging is needed.
Taking blood or bone marrow (aspirate/biopsy) may cause pain, bleeding, and/or bruising.

Contacts

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Scientific

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Diagnosis of symptomatic multiple myeloma (from IMWG see (Kyle, et al 2003)). All three of the following criteria must be met:
a). Monoclonal immunoglobulin (spike on electrophoresis, or band on immunofixation) on serum or on 24 hour collected urine (or demonstration of M protein in cytoplasm of plasma cell for non secretory myeloma)
b). Bone marrow (clonal) plasma cells or plasmacytoma
c). Related organ or tissue impairment (anemia, hypercalcemia, lytic bone lesions, renal insufficiency, hyperviscosity, amyloidosis or recurrent infections)
2. Subjects must have received at least two prior lines of therapy (including either bortezomib or lenalidomide) and be refractory to the most recent line of therapy according to the following definitions:
3. ECOG <= 2
4. Patients must have the following hematological laboratory values:
- ANC >= 1.5 x 109/L
- Hemoglobin >= 8 g/dl
- Platelets >= 75 x 109/L
- 24 -hour measured GFR CrCl >= 50 mL/min, or if not available, by serum creatinine < 2 x ULN)
- AST(SGOT) and ALT (SGPT) <= 2.5 x ULN
- Serum bilirubin <= 1.5 x ULN
- Serum albumin >= 2.5 g/dl
- Serum potassium, phosphorus, calcium and magnesium >= LLN,

- Normal thyroid function (TSH and free T4) (hypothyroidism correctable with supplements is allowed)
5. Baseline MUGA or ECHO must demonstrate LVEF >= the lower limit normal

Exclusion criteria

1. Prior therapy with an HDAC inhibitor
2. Impaired cardiac function, including: screening ECG with a QTc > 450 msec, congenital long QT syndrome, history or presence of sustained ventricular tachyarrhythmia, ventricular fibrillation or torsades de pointes, bradycardia (< 50 bpm), myocardial infarction or unstable angina <= 6 months prior to starting study drug, congestive heart failure (NYHA class III or IV), right bundle branch block or left anterior hemiblock and uncontrolled hypertension
3. Patients using medications that have a relative risk of prolonging the QT interval or inducing torsades de pointes
4. Concomitant use of CYP3A4 inhibitors
5. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of LBH589 (including diarrhea > CTCAE grade 1)
6. Other concurrent severe and/or uncontrolled medical conditions
7. Patients who have received radiation therapy, chemotherapy, any investigational drugs, immunomodulatory therapy or immunotherapy <= 3 weeks prior to starting study drug.
8. Patients who have undergone major surgery <= 4 weeks prior to starting study drug
9. Patients who have received high-dose steroids <= 2 weeks prior to starting study drug
10. Patients who have received high-dose corticosteroids as the only component of their most recent line of therapy

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	04-06-2007

Enrollment:	14
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	geen
Generic name:	geen

Ethics review

Approved WMO Date:	14-05-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-03-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2006-004087-31-NL
CCMO	NL16664.029.07