(ADMYRE: Aplidin - Dexamethasone in RElapsed/Refractory MYeloma) Randomized, Multicenter, Open-label, Phase III Study of Plitidepsin in Combination with Dexamethasone vs. Dexamethasone Alone in Patients with Relapsed/Refractory Multiple Myeloma.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON39027

Source
ToetsingOnline

Brief title
ADMYRE

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Kahler's disease, Multiple myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Pharma Mar
Source(s) of monetary or material Support: PharmaMar S.A.

Intervention

Keyword: dexamethasone, plitidepsin, Relapsed/refractory multiple myeloma

Outcome measures

Primary outcome

The primary efficacy variable for this study is PFS (Progression-free survival).

Safety variables for this study are:

- adverse events

- ECG

- LVEF (left ventricular ejection fraction), as evaluated by either

echocardiogram or multiple gated acquisition scan (MUGA)

- laboratory assessments

- physical examinations

- vital signs

Secondary outcome

Secondary efficacy variables are:

- Objective response rate (RR)

- Best overall response including rate of minor response (MR) or better

- RR to combination treatment in patients who crossed over after progression on

dexamethasone alone

- Time-to-event endpoint: duration of response (DR) and overall survival (OS)

- Intrapatient response and PFS comparison of patients who crossed over from

dexamethasone alone (group B) to plitidepsin plus dexamethasone combination

(group A).

Study description

Background summary

Despite recent advances in the treatment of multiple myeloma (MM), most patients ultimately relapse. The disease remains incurable and there is an urgent need for developing new therapeutic options including investigational drugs. The addition of corticosteroids to active new investigational drugs in MM is a major way to improve the outcome. The Sponsor is committed to the development of new drugs in an effort to broaden the spectrum of current antitumor therapies. Although the main mechanism of action by which plitidepsin inhibits cell growth and/or induces cell death remains to be fully characterized, several pre-clinical models suggest that the majority of the pharmacological activity of plitidepsin can be at least partially attributed to a combination of pro-apoptotic and antiangiogenic properties. The toxicity of plitidepsin in normal hematopoietic tissue is several folds lower than in tumor cells. Plitidepsin may display a positive profile for combination with other agents in chemotherapy regimens, avoiding overlapping toxicity.

Study objective

The primary objective is to compare the efficacy of plitidepsin in combination with dexamethasone vs. dexamethasone alone as measured by progression-free survival (PFS) in patients with relapsed/refractory multiple myeloma (MM).
Secondary objectives of this study are:
- To evaluate tumor response according to the International Myeloma Working Group (IMWG) criteria.
- To assess duration of response (DR) and overall survival (OS).
- To assess efficacy in patients who undergo crossover from dexamethasone alone to plitidepsin and dexamethasone combination.
- To characterize and compare the safety profile on both arms in this population.
- To characterize the pharmacokinetics (PK) and pharmacokinetic /pharmacodynamic (PK/PD) relationship.

Study design

Open-label, two-arm, 2:1 randomized phase III study. The efficacy of

plitidepsin in combination with dexamethasone vs. dexamethasone alone will be studied by means of PFS calculated using the IMWG uniform response criteria, and the evaluation of secondary efficacy endpoints. Patients in the control arm (dexamethasone alone, Arm B) who have documented disease progression according to Investigator*s criteria, after a minimum of eight weeks from randomization, should be offered crossover to the combination arm (plitidepsin + dexamethasone, Arm A) upon Sponsor agreement.
An Independent Review Committee (IRC) consisting of medical specialists directly involved in the care of patients with MM but not taking part in this trial as investigators or sub investigators, will review all efficacy data and will assign the date of progression/censoring and objective response according to their independent evaluation. This IRC will be blinded regarding to treatment arm allocation and identity of the cases reviewed.
An Independent Data Monitoring Committee (IDMC), including specialists in MM and in medical statistics, will evaluate the results of the protocol-specified analyses performed by an independent statistician, including efficacy assessments and safety information by investigators and IRC. Then, the IDMC will provide advice on the conduct of the study.

Intervention

Group A will be treated with a combination of plitidepsine infusions and oral dexamethasone, group B will only receive oral dexamethasone.
Group A treatment:
- Dexamethasone: 40 mg orally on Day 1, 8, 15 and 22 every four weeks (q4wk) at least one hour before plitidepsin infusion.
- Plitidepsin: 5 mg/m2 intravenously via a central venous catheter or in a peripheral vein over three hours on Day 1 and 15 of every 4-week cycle.
Group B treatment:
- Dexamethasone: 40 mg orally on Day 1, 8, 15 and 22 of every 4-week cycle.

Study burden and risks

Plitidepsin may cause several side effects, which are usually moderate in intensity and reversible. Based on data from previous clinical trials, side effects related to plitidepsin include those which are:
Likely (observed in >= 10% of patients):
- muscle cramps, muscle weakness or long-lasting muscular pain, mostly over shoulders and hips, elevated blood tests related to muscle damage
- fatigue, loss of appetite, nausea and vomiting, diarrhea, elevated blood tests relating to liver function
Common (observed in >=1% but in less than 10% of patients):
- allergic reactions
- gastrointestinal disturbances
Rare (observed in less than 1% of patients) but potentially serious:
- neutropenia/thrombocytopenia

Less frequently observed:
- heart problems (mainly arrhythmia, palpitations and pulse acceleration)
- venous thrombo-embolism
- lung embolism
Reproductive risks:
Because effects of plitidepsin during pregnancy have never been addressed formally neither in animals nor in humans, harmful effects cannot be excluded at this time and patients should therefore not become pregnant, or nurse a baby while participating in this study, and for at least six months after discontinuation of study treatment.

Dexamethasone may cause the following side effects:
Common:
- Muscle atrophy, pain or muscular weakness; delay in wound healing.
- Osteoporosis, compressive vertebral fractures, pathological fractures of long bones.
- Increased susceptibility to infections.
- Swelling, high blood pressure.
- Cataracts.
- Blood glucose increase.
- Nausea, vomiting, loss of appetite leading to weight loss, increased appetite leading to significant weight gain, diarrhea or constipation, inflammation of the pancreas, and irritation of the stomach.
- Headache or migraine, vertigo, insomnia, restlessness and increase of motor activity, and convulsions. Mood alterations, from euphoria to bad mood, depression and anxiety, and changes in personality to evident psychosis.
- Alteration of wound healing, atrophied and thin fragile skin, acne, increased sweating, excessive and increased hair loss in women, facial erythema, and hematomas.

Risk and side effects associated with the plitidepsin plus dexamethasone combination:
The plitidepsin plus dexamethasone combination has been evaluated in a previous, although small clinical study. The results of this previous study showed a similar overall safety profile, although this drug combination was associated with a slight increase in severe muscular side effects and a mild decrease in the incidence of transient and reversible severe transaminase increases in the blood (indicating liver damage).

Risks of study procedures:
There is a risk of infection, bleeding and/or swelling at the site of the cathether. Risks of blood drawing and bone marrow sampling include local pain, bruising, or infection at the site where the needle was inserted.
Additionally, risks associated with the radiation dose used for MUGA scans, radiographs for skeletal evaluation and CT.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

A patient is eligible for enrolment if all of the following criteria are met:
1. Age 18 years or older
2. ECOG Performance Status score equal or lower to 2.
3. Life expectancy equal to or higher than 3 months.
4. Patients previously diagnosed with multiple myeloma based on IMWG diagnostic criteria.
5. Patients must have relapsed or relapsed and refractory multiple myeloma after at least three, but not more than six, prior therapeutic regimens for MM, including induction therapy and stem cell transplant (regarded as only one regimen).
6. Patients must have received previous bortezomib-containing and lenalidomide-containing regimens (or thalidomide where lenalidomide is not available), unless unable to tolerate either of them.
7. Patients must have measurable disease defined as: a) For secretory MM: any quantifiable

serum monoclonal protein value and, where applicable, urine light-chain excretion equal to or higher than 200mg/24hrs. b) For oligo or non-secretory MM: presence of soft tissue (not bone) plasmacytomas, as determined by clinical examination or applicable radiographs, and/or by the presence of abnormal serum free light chains (sFLC): involved FLC level equal to or higher than 10mg/dl provided the serum FLC ratio is abnormal.
8. At least two-week washout period since the end of last therapy.
9. Adequate BM, renal, hepatic, and metabolic function assessed equal or less than 7 days before the study.
10. LVEF (left ventricular ejection fraction) door echocardiogram (ECHO) or MUGA scan above the lower limit of normal.
11. Negative pregnancy test (for woman of child-bearing potential). Both women and men must agree to use a medically accepted method of contraception throughout treatment period and for 6 months after discontinuation of treatment.
12. Voluntarily signed and dated written informed consent prior to any specific study procedure.

Exclusion criteria

A patient will not be eligible for this study if any of the following exclusion criteria are met:
1. Concomitant diseases/conditions:
a) history or presence of angina, myocardial infarction, clinically relevant valvular heart disease, cardiac amyloidosis or congestive heart failure within the last 12 months.
b) symptomatic arrhythmia (excluding anemia-related sinusal tachycardia grade equal or lower than 2), or any arrhythmia requiring ongoing treatment, and/or prolonged QT-QTc grade higher or equal to 2; or presence of unstable atrial fibrillation. Patients with stable atrial fibrillation on treatment are allowed provided they do not meet any other cardiac or prohibited drug exclusion criterion.
c) active uncontrolled infection.
d) morphological or cytological features of myelodysplasia and/or post-chemotherapy aplasia on BM assessment.
e) myopathy > grade 2 or any clinical situation that causes significant and persistant elevation of CPK (>2.5 xULN in two different determinations performed one week apart).
f) known human immunodeficiency virus (HIV) infection (HIV testing is not required unless infection is clinically suspected)
g. known active hepatitis B or C virus (HBV or HCV) infection.
h. limitations of the patient's ability to comply with treatment or follow up requirements.
i) any major other illnesses that will substantially increase the risk associated with the patient's participation in the study, as judged by the investigator.
j) peripheral neuropathy > grade 2
2. Women who are pregnant or breast feeding.
3. Concomitant medications that include corticosteroids, chemotherapy, or other therapy that is or may be active against MM, within 2 weeks prior to Cycle 1 Day 1. Concurrent corticosteroids are allowed, provided they are administered at an equivalent prednisone dose of less than or equal to 10 mg daily, as premedication for blood products only.
4. known history of peptic ulcer and/or major upper gastrointestinal bleeding episode

occurring during last year before study entry and/or related to prior steroid-based therapy.
5. Relevant history of mood-disturbances changes associated with previous steroid-based therapy.
6. disease-related symptomatic hypercalcemia despite optimal medical therapy.
7. known hypersensitivity to any involved study drug or any of its formulation components.

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):	21-12-2010
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aplidin
Generic name:	Plitidepsin
Product type:	Medicine
Brand name:	Fortecortin
Generic name:	Dexamethasone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-04-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-10-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-01-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-08-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-09-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	18-09-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-11-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2009-016138-29-NL
CCMO	NL32138.078.10