A phase II study of Vorinostat in patients with Polycythaemia Vera and Essential Thrombocythaemia

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1. To evaluate efficacy of vorinostat in the treatment of patients with polycythaemia vera (PV) and essential thrombocythaemia (ET) 2. To evaluate if vorinostat as monotherapy of patients with PV and ET is followed by a decline in clonal...

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

Summary

ID

NL-OMON36951

Source
ToetsingOnline

Brief title
Vorinostat in PV and ET

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
M. Vaquez-Osler, myeloproliverative diseases

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: bedrijven,Merck Sharp & Dohme (MSD),university of Copenhagen, dept. of hematology, Herlev Hospital

Intervention

Keyword: essential thrombocythemia, polycythaemia vera, Vorinostat, Zolinza

Outcome measures

Primary outcome

Hb, haematocrit, leukocyte count, platelet count.

Secondary outcome

Clinical symptoms of thrombosis or bleeding

bone marrow fibrosis

quantitiv JAK2 mutation status

Study description

Background summary

The aim of the present study is to evaluate the efficacy and safety of MK-0683 in the treatment of PV and ET. This agent has most recently been shown to be a potent inhibitor of the autonomous proliferation of haematopoietic cells of PV and ET patients carrying the JAK2 V617F mutation. Accordingly, it may be anticipated that MK-0683 - by decreasing the JAK2 allele burden - may influence clonal myeloproliferation and in vivo granulocyte, platelet and endothelial activation , which are considered to be major determinants of morbidity and mortality (thrombosis, bleeding, extramedullary haematopoiesis , myelofibrosis) in these disorders. The effects of MK-0683 at the molecular level will be studied by global/ focused gene expression profiling, epigenome profiling and proteomics.

Study objective

1. To evaluate efficacy of vorinostat in the treatment of patients with polycythaemia vera (PV) and essential thrombocythaemia (ET)
2. To evaluate if vorinostat as monotherapy of patients with PV and ET is followed by a decline in clonal myeloproliferation as assessed by conventional disease activity parameters (a decrease in the need of phlebotomy (PV) , leukocyte and platelet count)

Study design

Non-randomized, open-label phase II study . The inclusion period is 2 years.
Patient recruitment is planned from september 1, 2008.
Amendment 1: responding patients are permitted to continue after the drug has been paused as described in the main protocol, as long as safe and effective.
Extended treatment inclusion is expected until dec 2012

Intervention

Caps. Vorinostat a 100 mg , 400 mg/day for a maximum of 6 months. Amendment 1: extended treatment for a year; if safe and effective it might be longer.

Study burden and risks

11 visits, the first month every 2 weeks, after 1 month every 4 weeks.
bloodsamples every visit, at start an ECG, at start and after 6 months an abdominal ultrasound and bonemarrow biopsy
Amendment 1: visits will take place once every 4-12 weeks, every visit: bloodsamples (standard of care)

Contacts

Public
Vrije Universiteit Medisch Centrum

Boelelaan 1117
1081 HV Amsterdam
NL
Scientific
Vrije Universiteit Medisch Centrum

Boelelaan 1117
1081 HV Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

PV: 11. Male or female patient > 18 years of age and 2. A confirmed diagnosis of PV (see appendix 1) and 3. Biochemical evidence of active disease as defined by a) A need for phlebotomy within the last 3 months b) a leukocyte count > 10 x 109/L in the absence of infection or inflammation (normal CRP) and/or (PV/ET) c) a platelet count > 450 x 109/L in the absence of infection or inflammation (normal CRP) (PV/ET). ET: 1. Male or female patient > 18 years of age and 2. A confirmed diagnosis of high risk ET (see appendix 1) and 3. Biochemical evidence of active disease as defined by a) a platelet count > 450 x 109/L in the absence of infection or inflammation (normal CRP). PV + ET: 1. Newly diagnosed or previously treated patients in chronic phase or 2. Advanced phase PV or ET as defined by blasts of > 1 x 109/L in the peripheral blood and/or white cell count > 30 x 109/L or 3. Resistant or refractory PV or ET as defined by a haemoglobin < 10.5gm/dl with a platelet count > 600 x 109/L on current therapy or 4. Cycling platelet counts on therapy or 5. Intolerant to other therapies defined by patients with PV or ET who have side effects on current therapies preventing continuation (leg ulcers on hydroxycarbamide, unacceptable fatigue etc on interferon).

Exclusion criteria

1. A platelet count > 1500 x 109/L (a need for cytoreduction in platelet count) 2. Patients of childbearing potential without a negative pregnancy test prior to initiation of study drug. 3. Women who are breast feeding 4. Males and females not using contraceptives if sexually active. It is recommended that 2 reliable forms of contraception be used simultaneously unless abstinence is the chosen method of contraception. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as (a) surgically sterilized, or (b) postmenopausal, or (c) not heterosexually active for the duration of the study, or (d) heterosexually active and willing to use 2 birth control methods. The 2 birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1. A woman who is ???45 years of age and has not had menses for greater than 2 years will be considered postmenopausal. 5. ECOG Performance Status Score ??? 3 6. Serum creatinine more than 2 x???s the ULN 7. Total serum bilirubin more than 1.5 x???s the ULN 8. Serum AST/ALT more than 3 x???s the ULN 9. Interferon alpha within 1 week of day 1 10. Hydroxycarbamide within 1 week of day 1 11. Anagrelide within 1 week of day 1 12. Valproic acid (as an anticonvulsant) within 28 days of day 1 13. Any other investigational drug within 28 days of day 1 14. Active HIV, HBV or HCV infection. 15. Any serious concomitant disease or circumstances that could limit compliance with the study, including

but not limited to the following: CTCAE grade 3-4 cardiac general & arrhythmia, or psychiatric or social conditions that may interfere with patient compliance. 16. Any prior malignancy with the exception of cervical intraepithelial neoplasia, basal cell carcinoma of the skin, or other localized malignancy that has undergone potentially curative therapy with no evidence of that disease for five years, and who is deemed to be at low risk for recurrence by his/her treating physician. 17. Patient has a known allergy or hypersensitivity to vorinostat capsules.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-10-2009
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Zolinza
Generic name:	vorinostat

Ethics review

Approved WMO

Date:	19-06-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	12-08-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2011
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	EUCTR2007-005306-49-NL
ClinicalTrials.gov	NCT00866762
CCMO	NL27514.029.09