An Open-Label, Phase I Study to Evaluate the Pharmacokinetics and Tolerance of Co-administration of Oral Multiple Dose of Ketoconazole and an IV (bolus) Infusion of Eribulin in Patients with Advanced Solid Tumors

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Primary objective: To study the influence of repeated oral administration of ketoconazole, a potent CYP3A4 inhibitor, in a therapeutic dose on the plasma pharmacokinetics (PK) of eribulin administered via intravenous (IV) infusion.Secondary...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON33694

Source
ToetsingOnline

Brief title
NVT

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Cancer, Drug Metabolism

Research involving

Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Eisai Limited

Intervention

Keyword: Eribulin, Ketoconazole, Phase 1, Solid Tumors

Outcome measures

Primary outcome

Primary study parameter/outcome of the study: Pharmacokineticevaluation of

Eribulin when administered with Ketoconazol and without Ketoconazole.

Secondary outcome

Secondary study parameters/outcome of the study: Adverse event both by means of

laboratory research and by means of physical research and information of the

patient.

Study description

Background summary

Eribulin mesylate (E7389) is an anti cancer medicine, inferred from Halichonrin B, that mainly becomes metabolised through CYP3A4. For that reason it is necessary to research if Ketoconazol, a powerful CYP3A4 inhibitor, influences the metabolism of Eribulin.

Study objective

Primary objective: To study the influence of repeated oral administration of ketoconazole, a potent CYP3A4 inhibitor, in a therapeutic dose on the plasma pharmacokinetics (PK) of eribulin administered via intravenous (IV) infusion.
Secondary objective: To evaluate the safety and tolerability of eribulin when administered concomitantly with oral ketoconazole.
For the further investigation of the safety and tolerability of eribulin if

administered alone on days 1 and 8 of the 21-day scheme in patients with solid tumours.

Study design

Open label, phase I research in which patienten become randomised to determine the order of administeration of Ketoconazole with low dose eribulin either on day 1 or day 15

Intervention

Patients will be randomly allocated to one of two treatment sequences (group 1 or group 2).
Eribulin is administered as an IV infusion over 2-5 minutes, in the complete dosage of 1.4 mg/m2 if administered alone, but lowered to the dose level 0.7 mg/m2 if given on the same day as ketoconazole. Ketoconazole (200 mg) is administered once daily for 2 days, 1 hour before and 23 hours after the administration of eribulin on days on which both drugs are administered. See page 40 of the protocol for treatment schedule.

Study burden and risks

Until 4 weeks for the first treatment the screening phase takes place (after obtain of written consent). This exists from:
- Evaluation of in-and exclusion criteria
- Baseline tumour assessment according to RECIST criteria (this could possible cost an extra half day, if not yet present)
- ECOG, demography
- medical - and surgical history and treatment, including co-medication use
- physical examination, vital functions, length and weight
- ECG, blood - and urine assessments (including pregnancy test, if applicable)

The first treatment phase lasts 28 days. Patients are randomly assigned to group 1 or group 2. Eribulin is given on day 1 and day 15 and exists from two periods (eribulin only or with ketoconazole), followed by wash-out period of 2 weeks. Ketoconazole administration together with eribulin will be given in cycle 1 only.

On day 1 and 15 of cycle 1 (and further cycles), before medication is administered, it will be looked at:
- pregnancy test (if applicable)
- ECOG
- physical examination, vital signs, weight and body mass index
- adverse events evaluation, con. medication use
- blood - and urine assessments
- PK (pharmacokinetic) assessments will be done in cycle 1 only (totally 28

samples between day 1 and 7 and between day 15 and 21) :

Day 1/15: -0,5h for infusion, 15 min., 30 min., 60 min., 2h, 4h, 6h, 10h after infusion.
Day 2/16: 24 hours after infusion
Day 3/17: 48 hours after infusion
Day 4/18: 72 hours after infusion
Day 5/19: 96 hours after infusion
Day 6/20: 120 hours after infusion
Day 7/21: 144 hours done after infusion
Ketoconazole become only with eribulin in cycle 1 data.

Day 7 cycle 1/day 8 cycle 2:
- physical examination
- adverse event evaluation
- Co-medication use

Day 15-21:
- tumour assessment according to RECIST criteria
- ECG (only at the end of cycle 2)

Study termination (0-30 days after the last treatment amount or at termination):
- tumour assessment
- physical examination, vital signs, weight
- ECOG
- adverse events evaluation, co-medication use -
- blood - and urine assessment
- ECG

Common side effects of eribulin will be a decrease in the number of white and red blood cells in the body. A reduction in the number of white blood cells (neutropenia) can increase the risk of infection, including pneumonia, and urinary tract infections. A reduction in the number of red blood cells (anaemia) can result in a feeling of tiredness. Eribulin may also lower the number of platelets in the blood (thrombocytopenia). Thrombocytopenia can cause an increase in the risk of spontaneous bleeding and bruising. Other eribulin side effects include: loss of feeling or a tingling sensation in hands and feet (neuropathy), gastrointestinal problems such as vomiting, diarrhea and constipation. Nausea, on the other hand, is common. An unpleasant taste in the mouth and the development of sensitive areas such as ulcers in the mouth (stomatitis) and throat (mucositis) also occur rarely. Breathing problems, such as a feeling of tightness or breathlessness, and coughing are problems which arise on rare occasions. Other general, but rare, side effects may include: joint pain, fluid retention, weight loss, dizziness or headache. Fatigue and hair loss are, however, common.
Other unusual (very rare), but serious, side effects associated with eribulin

may include: increased heart rate, poorly functioning kidneys. abdominal pain and dehydration, deep vein thrombosis and pulmonary embolism.

Ketoconazole is a well known drug that can cause side effects such as nausea and vomiting, abdominal pain, diarrhea, headaches, dizziness, somnolence, rash and itchiness.
In very rare extreme cases, ketoconazole has caused: thrombocytopenia (low platelet numbers), allergic conditions such as anaphylactic shock, decreased hormone production (adrenocortical insufficiency), reversible increased intracranial pressure, dizziness, headache, loss of feeling in arms and legs (paraesthesia), sensitivity to light, jaundice, hepatitis, blood tests showing abnormal liver function, reddish uneven rashes (urticaria), itchiness, possible hair loss, erectile dysfunction, gynaecomastia and menstrual disorder.

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

1. Patients must have a histologically or cytologically confirmed solid tumour in an advanced stage that showed progression when standard therapy was followed or for which there is no standard therapy (including surgery or radiotherapy).
2. Resolution of all chemotherapy- or radiotherapy-related toxicities with a severity of class 1 or lower, except for stable sensory neuropathy <= class 2 and alopecia.
3. Patients must be >= 18 years old.
4. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2.
5. A life expectancy of >= 3 months.
6. Patients must have adequate renal function that must be apparent from serum creatinine <= 2.0 mg/dl (<= 176 µmol/l) or calculated creatinine clearance >= 40 ml/minute (min) according to the Cockcroft and Gault formula.
7. Patients must have adequate hepatic function that must be apparent from bilirubin <= 1.5 times the upper limit of normal (ULN) and alkaline phosphatase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <= 3 times the ULN, (in the case of liver metastases <= 5 times the ULN or in the case of bone metastases, the liver-specific alkaline phosphatase <= 3 times the ULN).
8. Patients must have adequate bone marrow function as demonstrated by means of absolute neutrophil count (ANC) >= 1.5 x 109/l, haemoglobin >= 10.0 g/dl or >= 6.2 mmol/l (a haemoglobin < 10.0 g/dl or < 6,2 mmol/l is acceptable if it is corrected by growth factor or transfusion) and blood platelets >= 100 x 109/l.
9. Patients must be willing and able to keep to the study protocol for the duration of the study.
10. Prior to any study-specific screening procedures whatsoever, patients must give written consent after receipt of information, on condition that the patient may withdraw his consent at any time without this having any consequences.

Exclusion criteria

1. Patients who have received any of the following treatments within the specified period before the start of treatment with eribulin:
a) Chemotherapy, radiotherapy or biological therapy within 2 weeks.
b) Hormonal treatment within 1 week.
c) Any study drug whatsoever within 4 weeks.
2. Patients receiving anticoagulant therapy with warfarin or related compounds, other than for good flow in the infusion line and who cannot be switched to heparin-based treatment cannot be considered. If a patient has to remain on a minidose of warfarin, the prothrombin time (PT) or international normalised ratio (INR) must be closely monitored.
3. Patients who at the time of the start of the study are receiving any medication, food supplements or other compounds or substances known to induce or inhibit the effect of CYP3A4, with the exception of ketoconazole.
4. Patients for whom the use of ketoconazole is contraindicated.
5. Patients receiving medications that might influence the metabolism of ketoconazole.

6. Pregnant or breast-feeding women; women of child-bearing age with a positive pregnancy test during screening or without a pregnancy test; women of child-bearing age unless (1) they have been surgically sterilised or (2) in the opinion of the investigator are taking adequate contraceptive measures. To be able to say of women that they are unable to have children, women who are perimenopausal must have been amenorrhoeic for at least 12 months.
7. Fertile men who are not willing to use contraception or fertile men with a female partner who is not willing to use contraception.
8. Patients whose intestinal absorption is affected.
9. Severe/uncontrolled intercurrent disease/infection.
10. Significant poor cardiovascular condition (history of congestive heart failure > New York Heart Association (NYHA) Class II, unstable angina or myocardial infarction in the last 6 months, or severe cardiac arrhythmia.
11. Patients with allogenic organ transplants who needed immunosuppression (with the exception of blood and blood component transfusions).
12. Patients with known positive human immunodeficiency virus (HIV) status.
13. Patients with brain or subdural metastases cannot be considered unless they have finished local treatment and have stopped the use of corticosteroids for this indication for at least 4 weeks before the start of treatment with eribulin.
14. Patients with meningeal carcinomatosis.
15. Patients with hypersensitivity to halichondrin B and/or halichondrin B-like compounds.
16. Patients with already existing neuropathy > Class 2.
17. Patients with other significant disease or disorders which, in the investigator*s opinion, might exclude the patient from the study.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2008
Enrollment:	12

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	N.v.t
Generic name:	Eribulin Mesylate
Product type:	Medicine
Brand name:	Nizoral
Generic name:	Ketoconazole
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-06-2008
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-10-2008
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-05-2009
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-03-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2007-005086-36-NL
CCMO	NL20914.031.08